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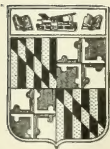
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GAUCHER'S DISEASE.

A REPORT OF TWO CASES IN INFANTS.

By J. H. MASON KNOX, JR., PH. D., M. D., H. ROSWELL WAHL, M. D., and HARRY C. SCHMEISSER, M. D., PH. D.

(From the Thomas Wilson Sanitarium, the Department of Pathology of the Western Reserve University Medical School, and the Departments of Pediatrics and Pathology of the Johns Hopkins University.)

The cases of Gaucher's disease reported in the following paper occurred in two children of the same parents that came under observation during a period of two years. The first child was admitted to the Thomas Wilson Sanitarium in the service of Dr. Knox. The disease ran a fatal course in a comparatively short time, the clinical and anatomical findings, the latter studied by Dr. Wahl, being prepared for publication in January, 1915. About one year before, the second child had been admitted to the Harriet Lane Home of the Johns Hopkins Hospital in the service of Dr. Howland. In this case also the clinical aspects were studied by Dr. Knox and an excised gland was examined by Dr. Wahl. The case likewise ran a rapidly fatal course and was studied anatomically by Dr. Schmeisser. It was decided to include the two cases in one report.

HISTORICAL.—Through the recent investigations, notably those of Bovaird, Brill, Mandelbaum, Libman, Reuben and others, the uncertainty surrounding the disease described by Gaucher in 1882 has been largely removed. It is now agreed that the term "Gaucher's disease" can be properly applied to only a small group of splenomegalies, namely, to those cases in which the organs show the presence of certain distinctive large cells. Of the total of 16 cases reported since 1882, 12 have been described in the last decade and three, exclusive of our cases, within two years. Unquestionably the condition is

more prevalent than has been suspected, and as the peculiar features of the disease become more generally known, the number of cases reported will probably increase rapidly.

The literature of the subject has been so thoroughly presented by Mandelbaum that a further review is unnecessary. It may be helpful, however, to present briefly in tabular form the instances of Gaucher's disease—proven to be such by microscopic examination—heretofore reported and to comment briefly upon the more important features. The cases accepted by Mandelbaum, together with two more recent ones, are summarized in the accompanying table (see pages 4 and 5), an analysis of which gives the following more important data:

ANALYSIS OF TABLE: *Sex.*—The disease appears to be more prevalent in the female. Of the 16 patients there were but three males.

Age.—It may manifest itself at any age, but the majority of cases reported have been in young adults. The oldest patient, Marchand's,* was a woman 44 years old; the youngest, Niemann's,† was a child of 14 months. It is probable that the condition in the older patients had existed for years before being recognized.

Symptoms.—The onset of the disease is insidious, the symptoms being vague and indefinite. A feeling of weight accompanying the enlargement of the abdomen was usually present.

Eleven of the patients had some form of hemorrhage, usually epistaxis or bleeding from the gums or into the skin. Dull abdominal pain was complained of in 10 instances. Edema of the feet was noted in four cases; in four there was fever and in four a moderate degree of dyspnoea. Three of the patients suffered from excessive sweating, and in several there was more or less indigestion. In all there was gradual loss of weight. Death ensued from exhaustion or from some intercurrent malady.

Physical Signs.—The most constant physical sign was the enlargement of the abdomen, due primarily to the increase in bulk of the spleen and liver.

Spleen.—The spleen is described as "filling the abdomen" in a number of instances. In Case 9 it reached a maximal size—45 x 25 x 13 cm.—and weighed 8100 gm. The relation of the spleen to the body weight, which is normally about 1:400, may in this condition be altered to 1:5 or 6. In each instance the organ retained its normal outline and was firm and resilient to palpation.

Liver.—Enlargement of the liver was noted in 14 cases. It was not so marked as was that of the spleen, and seemed to occur at a somewhat later period. The organ was firm and its shape was not altered.

Lymph Glands.—The superficial lymph glands were moderately enlarged in 10 instances, and in three additional cases certain internal groups of lymph glands were enlarged. In two cases the glands were not enlarged.

Color of the Skin.—Gaucher described his patient as having a skin of a peculiar leaden hue, which became more pronounced towards the end of the illness. A similar yellowish or brownish discoloration, most marked on the face and extremities, was noted in 11 cases. In two "slight jaundice" was mentioned, and in three cases no pigmentation was described.

Conjunctival Thickening.—Brill and Mandelbaum have described a "brownish-yellow wedge-shaped thickening of the conjunctiva" extending from the cornea to the inner and outer canthus. They consider this of diagnostic significance. This alteration in the conjunctiva has not been noted in the majority of the cases thus far reported, but its importance for diagnosis must be determined later.

Blood.—The blood presents the picture of a secondary anaemia of varying severity, dependent upon the course of the disease. In a few cases the red cells and the haemoglobin are only slightly altered. The most striking feature of the blood picture is the reduction in the number of leucocytes. This appears to be a constant finding. The minimal white count reported was 500 to the cubic millimeter. The differential count is usually within normal limits, and abnormal cells have been found only rarely in the circulating blood.

Family History.—The incidence of the condition in other children of the same parents is to be particularly noted. In many of these additional cases Gaucher's disease was not proven by pathological examination, but presumptive evidence of the condition was present, i. e., a large spleen and other important signs. The family history is recorded in 12 of the above cases,

and in nine of these an enlarged spleen and symptoms strongly suggesting the disease were found in one or more brothers and sisters of the patient. This tendency to appear in several members of the same generation is apparently a suggestive feature of the malady. In no instance was the disease transmitted from parent to offspring.

Cause of Death.—Gaucher's disease is essentially chronic and may last for years. Niemann's case and those we are about to describe—all in infants—suggest that the process is more intense in early life. Of the seven patients treated expectantly, two died from exhaustion after much emaciation, and five from intercurrent affections or from accident.

Splenectomy.—The spleen was removed in nine cases. Three of these patients died shortly after the operation. Six were reported living at various periods after the operation, one after 41 days, one after six weeks, three after five weeks, and one after 16 months. In most of these the sense of weight in the abdomen had been relieved, but there is no evidence that the further progress of the disease was arrested.

Syphilis and Tuberculosis.—An effort was made to determine whether syphilis or tuberculosis was concerned in the etiology of the condition. Of the 16 cases no evidence of syphilis was found at autopsy in two instances; in five others the Wassermann test was negative; in only one (Niemann) was it positive. In 13 of the 16 cases no tuberculosis was found on examination of the organs or of the excised spleen. Tuberculous lesions were present at autopsy in three instances. It can be confidently assumed that neither syphilis nor tuberculosis plays an etiological rôle in this disease.

Microscopical Findings.—In each instance the presence of peculiar, pale round or oval cells, having an average diameter of from 20 to 40 microns and one or several relatively small nuclei, is the characteristic feature of the disease. In many of the cells the protoplasm stains poorly, is finely granular and vacuolated. Their relative number varies greatly, depending apparently upon the severity of the process. In some instances they occupy almost the entire organ; or they may be found singly or in groups among the normal cells. The spleen, liver and lymph glands are most frequently involved, although the bone-marrow and, as in our cases, nearly all the tissues of the body may be affected.

Origin of the Cells.—The origin of these cells has been much discussed and will be referred to in detail later on in the paper. The views thus far held are that they arise either from the reticulum or from cells lining the blood and lymph vessels.

Pathogenesis.—The cause of this remarkable condition is as yet unknown. It has no connection with a neoplastic growth, as Gaucher at first thought. No evidence of a bacterial or protozoan infection has been found. A number of writers have considered the disease dependent upon a chronic intoxication of an undetermined nature.

CASE I.—S. G., a white female infant, 9 months of age, was admitted to the Thomas Wilson Sanitarium June 12, 1912.

Family History.—The father, a moderate user of alcohol, was 41 years of age and well. The mother was 38 years of age and

well. Both parents were Russian Hebrews of small means. They had had 11 children, as follows:

1. A girl, 20 years, well.
2. A boy, died at 8 months, cause unknown.
3. A boy, 18 years, well.
4. A boy, died at 14 years of hip disease.
5. A girl, 14 years, well.
6. A girl, died at 1 year, "smothered in bed."
7. A boy, 11 years, well.
8. A girl, died at 18 months of convulsions.
9. A boy, 6 years, well.
10. A girl, 4 years, well.
11. A girl, the patient.

Past History and Present Illness.—The patient's birth was spontaneous. She was breast-fed for one month and then given a cow's milk mixture. She never thrived. For a month or two she vomited frequently, but for three months the milk was well retained. She slept well; cut two teeth at six months and was never acutely sick. The gain in weight, however, was very slow. The stools were from two to four in 24 hours, yellow and formed.

Physical Examination.—On admission the patient weighed 11 pounds. She was considerably emaciated. The skin was pale, with a slight brownish pigmentation, more marked on the face and arms. The abdomen was prominent; the cervical and axillary glands were slightly enlarged. The lungs were clear. The heart was not enlarged. There was a soft systolic murmur heard at the apex. The upper border of the liver began at the 6th rib and extended 2½ inches below the costal margin in the right nipple line. The surface of the liver was smooth and firm and the notch was readily palpable. The spleen was represented by a large mass extending 4½ inches below the left costal margin to the level of the umbilicus. The surface was firm and a little rough; the notch was palpable. The kidneys were not felt. The reflexes at the knee were present.

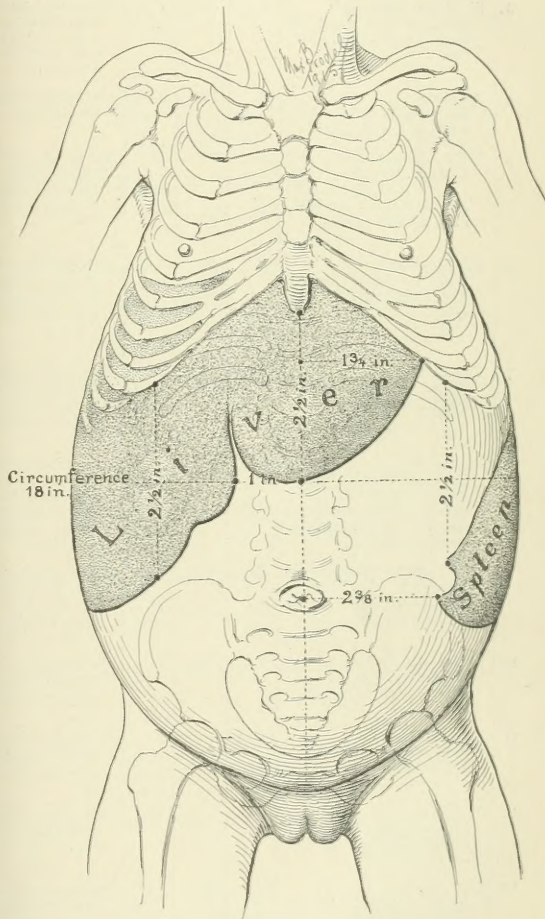
The blood examination on admission was as follows: Leucocytes, 10,400; red cells, 5,200,000; hæmoglobin, 90%. Differential count: Polymorphonuclears, 42%; large mononuclears, 5%; small mononuclears, 41%. Examination of the stools showed an excess of fatty acid crystals but no bile. During the first month after admission the child gradually lost in weight. On July 12, 1915, the blood condition was as follows: Red cells, 4,400,000; leucocytes, 25,400; hæmoglobin, 60%. Differential count: Polymorphonuclears, 59%; large mononuclears, 3.2%; small mononuclears, 36%; transitionals, 1%; myelocytes, 1%. The Wassermann and Von Pirquet tests were negative.

The patient continued to lose strength and weight. She was given a milk mixture successfully. There were from two to four fecal stools in 24 hours and no fever. There was a continuous loss of weight to 8½ pounds and death resulted from exhaustion at the age of 11 months, two months after admission to the sanitarium. The day before death a marked change took place in the differential count of the leucocytes. Their total number was increased to 35,000. The differential count was: Small lymphocytes, 82%; large lymphocytes, 9%; large mononuclears, 5%; polynuclears, 3%; unclassified, 1%.

AUTOPSY (four hours after death).—The body is that of a very emaciated white female infant 61 cm. long. The external ear contains a dried hemorrhagic discharge. The abdomen is very prominent. The veins are distended, but there is no caput Medusæ. The outlines of the lower edge of the liver and of the spleen are visible through the thin abdominal wall, the notches being easily recognized. The inguinal glands are considerably enlarged and are firm. The peritoneal cavity contains no excess of fluid. The liver extends 7 cm., the spleen 5.5 cm., below the costal margin. The heart weighs 25 gm., and shows no gross abnormalities. The lungs are voluminous, but everywhere contain air. In the lower right lobe the tissue feels denser and

tougher than elsewhere and the pleura is a little more prominent. On section this part of the lung tissue is subdivided into small lobules by dense bands of fibrous tissue.

The liver is considerably enlarged and weighs 415 gm. It has a pale, grayish-pink color. Its surface is smooth and glistening and the capsule is not thickened. The lobules appear through the capsule as minute, pink dots surrounded by a pale yellow periphery. On section the organ cuts with a slightly increased



GAUCHER'S DISEASE—CASE I.—Diagram showing enlargement of liver and spleen. July 1, 1912.

resistance and shows a pale yellow or a slightly mottled grayish-yellow, moist surface, from which a thick yellowish mucoid material can be easily scraped off. This material does not feel greasy, but resembles condensed milk in consistence. There is a slight patchy fibrosis. The gall-bladder is small and contracted, containing about 1 cc. of thin yellow bile. The bile passages are patent. The common bile-duct is partly surrounded by three firm lemon-yellow lymph nodes, from 3 to 8 mm. in diameter.

No.	Author and Reference.	Sex.	Age at death.	Age at onset.	Chief Symptoms.	Physial Signs.		
						Spleen.	Liver.	Lymph glands.
1	Gaucher: Thèse de Paris, 1882.	F	30	7	Never robust; epistaxis, irregular menses, enlargement of abdomen. In last months, bleeding from gums, abdominal pain, œdema of feet, fever.	51 × 25 cm. (by palpation). Weight, 4700 gm.	Extends to umbilicus. Weight, 3500 gm.	Enlarged slightly.
2	Collier: Tr. Path. Soc. London, 1895, XLVI, 148.	F	6	2	Never robust; enlargement of abdomen, epistaxis, emaciation, subnormal temperature.	Weight, 2070 gm.	Not palpable, mesenteric glands large.
3	Picou and Raymond: Arch. de méd. expér. et d'anat. path., 1896, VIII, 168.	F	32	4	Abdominal pain, from 4th year, menorrhagia, bleeding from gums, œdema of ankles, fever, loss of weight, enlargement of abdomen.	"Filled abdomen."	Three finger-breadths below costal margin.	Enlarged at hilus of spleen.
4	Bovaird: Am. Jour. Med. Sc., 1900, n. s., CXX, 377.	F	13	3	Increasing enlargement of abdomen, shortness of breath.	Weight, 6250 gm.	Not enlarged.	Enlarged slightly.
5	Brill, Mandelbaum and Libman: Proc. New York Path. Soc., 1904, IV, 143; Am. Jour. Med. Sc., 1905, n. s., CXXIX, 491.	M	30	14	Sweating, epistaxis, enlarged spleen, pain in splenic region and in legs, petechial hemorrhages, dyspnea.	Weight, 5280 gm.	Weight, 4800 gm.	Enlarged in thorax and abdomen.
6	Schlagenhauser: Virchows Arch. f. path. Anat., 1907, CLXXXVII, 125.	F	43	5	Enlargement of abdomen, œdema of feet, bleeding from gums, epistaxis, increasing weakness, pain over liver.	31 × 20 × 12 cm. Weight, 3510 gm.	Weight, 3000 gm.	Enlarged.
7	Von Herzel: Wien. klin. Wchnschr., 1907, XX, 123.	F	37	31	Epistaxis, during childhood. At 31 years, abdominal pain, vomiting, enlargement of abdomen. Later, chills and sweating.	32 × 16 × 12 cm. Weight, 3000 gm.	Extends a "hand-breadth" below costal margin.	Enlarged slightly.
8	Marchand: München. Med. Wchnschr., 1907, LIV, 1102; also Resel: Beitr. z. path. Anat. u. z. allg. Path., 1909, XLVI, 241.	F	44	24	Pain in abdomen at 24 years. At 35 years, great weakness, myomatous uterus, ovarian tumor. Later, increased weakness, cachexia, hemorrhages in skin.	41 × 15 cm. Weight, 2720 gm.	24 × 26 cm. Extends 3 finger-breadths below costal margin.	Enlarged.
9	Brill, Mandelbaum and Libman: Am. Jour. Med. Sc., 1909, n. s., CXXXVII, 849.	F	42	21	At 21 years noticed abdominal tumor, sweating, hemorrhages of the skin, anemia, emaciation, epistaxis, bleeding from gums and bowel, dyspnea.	45 × 25 × 13 cm. Weight, 8100 gm.	35 × 30 × 12 cm. Weight, 3900 gm.	Enlarged slightly.
10	de Josselin de Jong u. van Heukelom: Beitr. z. path. Anat. u. z. allg. Path., 1910, XLVIII, 598.	F	12	7½	Enlargement of abdomen, weakness, bleeding from gums, attacks of syncope, vomiting.	Reaches to symphysis pubis.	Extends 2 finger-breadths below costal margin.	Not enlarged.
11	Mandelbaum: Jour. Exper. Med., 1912, XVI, 797.	M	4½	3	Enlargement of abdomen, slight abdominal pain, epistaxis, increasing languor.	18 × 9.5 × 5 cm. Weight, 490 gm.	Extends 3 finger-breadths below costal margin.	Much enlarged.
12	Wilson: Surg., Gynec. and Obst., 1913, XVI, 240.	F	27	12	Frequent digestive disturbance, anemia, abdominal pain, œdema.	Weight, 5280 gm.	Extends 3 inches below costal margin.
13	Downes: Med. Rec., 1913, LXXXIII, 697.	F	28	13	Enlargement of abdomen, loss of appetite, headache, emaciation, dyspnea.	35 × 13.5 × 6.5 cm. Weight, 1813 gm.	Extends 1 inch below costal margin.	Not enlarged.
14	Niemann: Jahrb. f. Kinderh., 1914, LXXVIX, 1-10.	F	17 mo.	2 mo.	Never thrived; indigestion, pallor, enlargement of abdomen, œdema of eyelids and feet, low irregular fever.	Extends below level of navel.	Extends to 1 cm. above ant. sup. spine.	Enlarged slightly.
15	Erdman and Moorhead: Am. Jour. Med. Sc., 1914, n. s., CXLVII, 213.	F	3½	14 mo.	Healthy infant, large spleen noted at 14 months. From this time nervous indigestion.	Extends to level of umbilicus.	Extends 2 finger-breadths below costal margin.	Inguinal glands enlarged.
16	Herrman, Roth and Bernstein: Arch. Pediat., 1914, XXXI, 340.	M	14	4	Large spleen noted at 4 years, abdominal pain, epistaxis, hematemesia, bleeding from gums, asthenia.	27 × 13 × 10 cm. Weight, 1320 gm.	Extends 5 cm. below costal margin.	But little enlarged.

Blood Examination.	Family History.	Treatment.	Result and cause of death.	Histological Findings.	Remarks.
R. B. C.: 2,281,000 W. B. C.: 3,600, in last months.	Unknown.	Expectant.	Died. Tuberculosis, pulmonary and intestinal.	Spleen: Parenchyma replaced by large irregular cells with pale-staining cytoplasm in connective tissue spaces. Liver: Cirrhosis (?).	Condition unlike any known form of splenic hypertrophy.
.....	One sister, enlarged spleen; three other children died of tuberculosis.	Expectant.	Died. Bronchopneumonia; no tuberculosis.	Spleen: Characteristic cells. Lymph glands: do.	No note on bone-marrow, liver or adrenals.
R. B. C.: 1,300,000 After operation: W. B. C.: 20,000 Dif. count, normal.	No similar cases.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells. Lymph glands: do.	No note on other tissues. Case similar to Case 1.
R. B. C.: 2,880,000 W. B. C.: 4,000 Hb.: 60%	One sister, enlarged spleen and liver.	Splenectomy.	Died three hours after operation.	Spleen: Characteristic cells. Lymph glands: do. Liver: Cirrhosis with do. Adrenal: A few do.	No note on bone-marrow.
At 15 years: R. B. C.: 5,000,000 W. B. C.: normal. Later: W. B. C.: 4,000 Hb.: 45%	Four out of six brothers and sisters had same condition.	Expectant.	Died. Exhaustion, pericarditis.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.
At 43 years: R. B. C.: 4,700,000 W. B. C.: 1,300 Later: W. B. C.: 800 Dif. count, normal. Hb.: 65%	One sister has large spleen; five children of parents well.	Expectant.	Died. Tuberculosis, pulmonary and glandular.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone-marrow: do.	Disease said to involve lymphaticohematopoietic system, due to poisoning; possibly tuberculosis.
At 37 years: R. B. C.: 4,200,000 W. B. C.: 7,000 Dif. count, normal. Hb.: 92%	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Constant abdominal pain after operation. Liver still large.
"No leucocytosis."	No history of similar condition in family.	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do. Bone-marrow: do.	Ascites noted.
R. B. C.: 3,500,000 W. B. C.: 3,600 to 5,200 Dif. count, normal. Hb.: 35%	Brother of Case 5; four out of six brothers and sisters had the same condition.	Expectant.	Died. Fracture of skull.	Spleen: Characteristic cells. Liver: do. Lymph nodes: do. Bone-marrow: do.	More abdominal process than in Case 5. No tuberculosis.
R. B. C.: 4,700,000 W. B. C.: 3,800 Dif. count, normal. Hb.: 65%	Three sisters and one brother had large spleens; seven brothers and sisters well.	Splenectomy.	Living five months after operation.	Spleen: Characteristic cells.	Wassermann and von Pirquet, negative.
R. B. C.: 2,208,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 35%	One sister has large spleen; one sister has large liver; two children are well.	Splenectomy.	Died one day after operation.	Spleen: Characteristic cells. Liver: Cirrhosis and do. Lymph glands: do. Bone-marrow: do.	Wassermann negative. No tuberculosis.
R. B. C.: 5,200,000 W. B. C.: 4,800 Hb.: 80%	Splenectomy.	Died 12 hours after operation.	Spleen: Characteristic cells.	Two other cases reported, thought by Marchand not to be Gaucher's disease.
R. B. C.: 3,840,000 W. B. C.: 1,400 to 900 Dif. count, normal. After operation: W. B. C.: 16,000	No history of similar condition.	Splenectomy.	Living 41 days after operation.	Spleen: Characteristic cells; not so extensive transformation as in other cases.	Probably a comparatively early case. Wassermann negative. Wedge-shaped thickening of conjunctiva.
Blood said to be normal in R. B. C., W. B. C. and Hb.	Expectant.	Died. Exhaustion.	Spleen: Characteristic cells. Liver: do. Lymph glands: do.	Wassermann positive. Extensive changes, very similar to those in our cases.
R. B. C.: 5,000,000+ W. B. C.: 10,000 Dif. count, normal. Hb.: 80%	One brother died with large spleen; two brothers well.	Splenectomy.	Living after 16 months.	Spleen: Characteristic cells.	Wassermann negative.
R. B. C.: 3,000,000 to 4,000,000 W. B. C.: 5,000 Dif. count, normal. Hb.: 45%	One sister, next in age, had a large spleen; seven children well.	Splenectomy.	Living after six weeks.	Spleen: Characteristic cells.

The *spleen* weighs 86 gm. and measures 13x5x4 cm. The surface has a mottled, patchy, grayish-pink color. The organ feels firm and its edges are rounded. The surface is smooth and glistening. The capsule is slightly thickened. On section the organ cuts easily and the splenic pulp is friable. The cut surface is rather moist and shows numerous red, slightly translucent areas, 1 mm. in diameter, surrounded by a soft, faint reddish-yellow peripheral zone that can be scraped out quite easily and resembles the material removed from the liver, although in the spleen it has a pinker appearance. There is no marked increase in the fibrous tissue.

The *pancreas* shows no pathological changes. The *kidney cortex* is slightly swollen and has a pale yellow color. The striations are poorly defined. The *adrenal glands* are considerably enlarged, each weighing 5.5 gm. On section a considerable amount of a brick-red fluid escapes from the medulla. The latter is large and prominent and has a pale yellow color. The cortex appears normal, though its yellow color is quite marked. In the mucous membrane of the stomach, near the pylorus and projecting 3 mm. above the surface, is a firm nodule 0.5 cm. in diameter, from which a gray mucoid material can be expressed. The intestinal mucosa shows congestion and a few small ecchymoses. The Peyer's patches are swollen. The appendix is rather large, but otherwise normal. The solitary follicles of both the small and large intestine are enlarged and surrounded by a narrow zone of congestion. The pelvic organs show nothing abnormal. There is a general enlargement of all the lymph glands, though the epitrochlear and other superficial nodes, except the inguinals, were not felt. They present a uniform appearance, being more or less bright yellow in color. They are quite firm and cut with a slightly increased resistance. On section a moderate amount of pale yellow viscid material escapes from the central part of most of the glands. The largest glands are near the head of the pancreas, measuring 1.5x2 cm. The thymus has an unusually pale yellow color, but otherwise is normal in size and appearance.

MICROSCOPICAL FINDINGS: *Heart.*—Many of the nuclei of the heart muscle are surrounded by a clear zone. Vacuoles of varying size, usually very small, are numerous in the muscle fibers. In some areas, where the fibers are cut in cross-section, the vacuoles are so numerous that the tissue resembles a markedly fatty liver. These vacuoles stain neither with Sudan III nor with osmic acid.

Lungs.—Most of the lung tissue appears normal. The air sacs contain a few desquamated epithelial cells. There is, however, a peculiar swelling of the cells of the interstitial tissue which gives them a finely vacuolated appearance. As indicated in the macroscopical report, the pleura over the lower lobe is thickened, and broad bands of loose connective tissue pass in, dividing the lung tissue into regular, well-defined lobules. The interstitial tissue is very much thickened and infiltrated with lymphocytes, swollen cells, many of which have a vacuolated protoplasm, and young connective-tissue cells. The connective tissue about the bronchi and the vessels is markedly increased. Surrounding the muscularis of some of the small arterial twigs there are several concentric rows of markedly swollen, pale, vesicular or granular cells, similar to, if not identical with, the large pale cells of the spleen and lymph nodes. The lumina of these vessels are often completely obliterated. The air sacs contain many large, irregularly round, faintly pink-staining, granular or vacuolated cells with a small nucleus, rich in chromatin; these resemble somewhat the large pale cells of the liver and spleen. They also resemble closely the swollen, partly degenerated cells in the air vesicles.

Liver.—The capsule is not thickened. The lobulation is well marked in some areas and obscure in others. In the former there is a considerable increase in the fibrous tissue of the portal spaces with extension into the lobule. The intralobular architecture is

entirely obliterated, the normal arrangement of liver cells in columns, radiating from the central vein, being replaced by an irregularly distorted conglomeration of large polygonal or irregularly round, granular cells of two types. The cytoplasm of the predominating type stains deeper and shows coarse protoplasmic granules and numerous small vacuoles. The cells of the other type frequently appear to be inserted between those of the first, and are distinguished by their very faintly staining, finely granular or vacuolated cytoplasm. They suggest swollen endothelial cells, whereas the darker-staining cells resemble swollen transformed liver cells. In both cases the nucleus is relatively small, stains rather deeply, and may contain one or two definite chromatin granules. Although in most of the cells the cytoplasm is granular, in some there are many vacuoles, which are usually small, though large ones occur. In other cells the cytoplasm may contain vacuoles of various sizes; it may present a streaked appearance or may be concentrated into a small area in an otherwise vacuolated cell. No normal hepatic cells are present. A few elongated or oval cells with a finely granular or vacuolated cytoplasm are embedded in the fibrous tissue of the portal spaces, especially where there is considerable fibrosis.

Spleen.—The most striking change in the spleen is the replacement of the lymphoid cells by large cells separated into clusters and columns by very prominent sinusoids. The lymphoid cells and splenic pulp cells are present only about the Malpighian bodies, which are also being infiltrated with these large pale cells. The latter tend to group first in the center of the corpuscle. A few lymphocytes are occasionally present in or about the sinusoids. The capsule and trabeculae are slightly thickened and strands of fibrous tissue extend into the parenchyma of the organ. The Malpighian bodies are diminished in number and show a striking tendency to be replaced by large cells—the process beginning in the center of the Malpighian body and progressing peripherally. These large, round, oval or polygonal-shaped cells usually have a faintly staining granular and vacuolated cytoplasm. The reticulum encloses clusters of these cells. Frequently strands of reticular fibrilla occur between the individual large cells. Some of the large, pale cells lie free in the reticular spaces. They may contain two, rarely three, nuclei. A few of the large, pale cells contain red cells or nuclear fragments. This phagocytosis is not frequent. The endothelial cells of the sinusoids are markedly swollen and mitotic figures may occasionally be seen. All transitional stages occur between the large, swollen endothelial cells and the very large pale, finely granular cells lying free or attached to the wall of the sinusoids. Blood pigment is present, especially in the large, pale cells about the Malpighian bodies.

Pancreas.—Many of the cells of the islets appear swollen and granular and small vacuoles are frequent in the cytoplasm. In the interlobular connective tissue there are a few small foci of large, rounded, vacuolated, endothelial cells; otherwise nothing abnormal is noted.

Kidneys.—The capsule is not thickened and the interstitial tissue is not increased. The epithelial cells of the convoluted tubules are swollen; the cytoplasm is granular and often contains small vacuoles. The glomeruli are prominent. The cells in the capillary tuft tend to become swollen, and their cytoplasm is often distinctly vacuolated. Occasionally, two or more of these cells may become so much enlarged and filled with vacuoles that they appear identical with the large, pale cells of the spleen.

Adrenals.—In the cortex the cytoplasm is granular and is often undergoing a vacuolar or oedematous change, especially in the outer zone. The medulla is very much enlarged and is the seat of a peculiar change which, in some areas under the low power, gives it the appearance of adipose tissue, owing to the replacement of the medullary cells by large, irregularly rounded, granular or vacuolated cells embedded in a coarse reticulum. On higher magnification these large cells have a granular or vacuolated foamy

cytoplasm and a small nucleus; they seem to be identical with the large cells described in the spleen. In some areas the medulla has the appearance of a very wide-meshed, irregular reticulum, the spaces of which contain a granular or vacuolated cytoplasm more or less completely subdivided by cell outlines and containing deeply stained, scattered nuclei. The cells lie without the blood-vessels and sinuses, and usually fill the reticular spaces in which they occur. In some sections there are a few more or less compressed cords of medullary cells separated from the cortex by a larger or smaller zone of the large, pale, foamy cells.

Gastro-intestinal Tract.—Vacuoles are frequent in the epithelial cells of the mucosa and in many of the stroma cells. The epithelium of the intestinal villi has, for the most part, desquamated; the tunica appears edematous and contains some polymorphonuclear leucocytes and lymphocytes. Large, pale, slightly foamy cells occur in the stroma between the glands. These are especially abundant between the glands of the appendix and resemble the large, pale cells of the spleen. In the cecum the serous surface is partly covered by a flat layer of lymphoid tissue, within which are many large, pale granular cells, identical with those of the spleen and lymph nodes. Beneath the serosa and between the different layers of the small intestine small foci of similar large, pale cells occur.

The *thymus* is distinctly lobulated. The lymphoid cells have disappeared except in the immediate vicinity of, and where they radiate from, Hassall's corpuscles. Numerous large, pale, granular or vacuolated cells, similar to those of the spleen, are embedded in a wide-meshed reticulum. They occur singly and in clusters. None of these cells are seen in the capillaries or lymph sinuses. The *lymph glands* present a variable appearance, but in all of them there has been a more or less extensive replacement of the lymphoid cells by the pale granular cells described in the spleen. In some sections there are comparatively few of these large cells, and they are most abundant in the medullary portion of the node. In other sections practically all of the lymphoid cells have disappeared, giving the appearance of an endothelial tumor, except that the normal architecture and framework of the gland is still intact. The peripheral and medullary sinuses are easily recognized, and are more or less filled with large, pale, rounded cells. All intermediate stages between these two may occur. In some of the glands there are irregular bands of young cellular connective tissue in which vacuoles occur. The large, pale cells appear to develop first in the medullary part of the gland. Some of these cells show phagocytosis of red blood cells and leucocytes. In the later stages the cells appear in the lymphoid foci and in the peripheral sinuses. In the late stages the lymph and blood sinuses are very prominent and the lining endothelial cells show all transitions to the large, pale, vacuolated cells occurring in the spleen. Mitosis is occasionally seen in these endothelial cells. In other portions these cells appear to be closely related to the reticulum. They are usually rounded or polygonal in shape and contain a considerable amount of granular protoplasm, which tends to be vacuolated or foamy, and a rather small nucleus rich in chromatin. The cells are arranged in alveoli bounded by reticulum or by blood-vessels or sinuses. The connective tissue is not markedly increased in any of the lymph nodes, though in the larger glands the large, pale cells are separated into distinct lobules by strands of fibrous tissue. There is no blood pigment present. The large, pale cells infiltrate all of the lymphoid foci of the alimentary tract, but the lymphoid cells always predominate. This is especially well marked in the flattened mass of lymphoid tissue on the serous coat of the cecum, in the solitary lymph follicles of the large and the small intestine, in the lymphoid tissue of the appendix and in minute lymph nodes near the intestine.

Special Microscopical Technique.—Examination of frozen sections of material fixed in formalin shows the presence of a homogeneous, slightly refractile substance in the large, pale granular

or vacuolated cells. It fills the vacuoles in the protoplasm noted in the paraffin and colloidal sections. It is not as readily removed by ether as by absolute alcohol. This substance in the large, pale cells reacts in a peculiar but distinctive way to the fat stains. With scarlet red the large cells show many minute, faint orange-staining droplets. In some cells more of the dye is taken up; in others a few of the droplets take a deep orange-red color. The same results were obtained with Soudan III. In both cases the fat control section stained a deep orange-red. With Nile-blue sulphate the large cells took a faint violet, pale blue, or pink color, which in chromated sections changed to a deep blue, while the fat in the control section stained bright red and the fatty acid stained purple or blue. With osmic acid the homogeneous substance in the large, pale cells stained either faintly gray or not at all. It was stained black with the Weigert-Pal myelin sheath stain and was doubly refractive in many of the cells. Some of the large cells took a dirty, reddish-brown color with scarlet red. In the liver, spleen and lymph nodes there were scattered large, pale cells more or less filled with droplets of neutral fat. These were especially abundant in the thymus. The large cells, embedded in the periportal fibrous tissue of the liver were mostly filled with droplets, staining red with scarlet red. The cortical cells of the adrenal gland were more or less filled with red-staining droplets, after treatment with scarlet red, standing out in sharp contrast with the non-staining or pale orange droplets filling the large, pale cells in the medulla. In the kidney most of the large, pale cells in the glomerular tufts contained red-staining droplets after treatment with scarlet red, but did not stain with osmic acid. A few scattered droplets of neutral fat were present in the epithelium of the convoluted tubules. The vacuoles noted in the heart muscle did not stain with any of the fat dyes. After treatment with Ciacio's and also with Bell's stain for lipoids, some lipid droplets were present in the large, pale cells. In most of the organs, especially in the liver, spleen and lymph glands, there were all transitions between cells that did not stain at all and those which contained deep orange-staining droplets after treatment with scarlet red. These varying reactions to the different methods for the demonstration of fats and lipoids in tissues suggest the presence of some fat-like substance, within the large, pale cells, that may be in the process of transformation into neutral fat and possibly represent an intermediate stage between the latter and a closely bound molecule of proteid and fat.

CASE II.—On February 11, 1914, the mother of the former infant (Case I) brought to the out-patient department of the Harriet Lane Home another female infant, S. G., 5 months of age, and remarked that this baby had the same disease as her sister, who had died 20 months before. The similarity in appearance of the two infants was striking.

Past History and Present Illness.—The patient's birth was normal. She was exclusively breast-fed. She had always been thin and sickly, but presented no symptoms of any acute disorder. She was brought to the clinic because of her weak and emaciated condition.

Physical Examination.—The patient was much emaciated. She weighed 9 pounds. The temperature was 96.4° F. The skin had a grayish-yellow color. There was no general glandular enlargement. The right lung was clear. There was slight impairment and a few moist râles at the base of the left lung. The heart sounds were clear. The abdomen was full, measuring 14 inches in circumference. The superficial abdominal veins were dilated. The liver was enlarged and firm and extended 2½ inches below the costal margin, from the sixth interspace. The spleen was enlarged, firm in consistence, and reached 2½ inches below the costal margin, extending slightly below the level of the umbilicus. The cervical glands were palpable; the inguinal and axillary glands were slightly enlarged. The reflexes were normal, as were also the electrical reactions. Slight lateral nystagmus was noted.

The patient returned occasionally to the clinic, but her condition remained unchanged. In May the blood condition was as follows: Red blood cells, 3,024,000; white blood cells, 11,240; hemoglobin, 65%. Differential count: Polymorphonuclear cells, 34%; lymphocytes, 60%; transitionals, 3.5%; eosinophiles, 1%; basophiles, 1.5%. The Von Pirquet and Wassermann tests were negative.

The patient was admitted to the Harriet Lane Home May 18, 1914, the condition being practically unchanged. On July 22, the temperature rose to 102° F., and continued irregularly elevated. In August a number of furuncles developed. In September a sharp rise in temperature was occasioned by an otitis media, secondary to a nasopharyngeal infection. The leucocytes varied from about 18,000 to 22,000, the differential count showing polymorphonuclear cells, 31%; mononuclear cells, 67%. On October 29, the patient was given a treatment with radium applied over the splenic area.

On October 21, some lymphatic glands from the neck and axilla were excised. Microscopic examination of the sections showed that a considerable number of areas of the gland were occupied by the large, round, oval endothelial-like cells, known to be characteristic of Gaucher's disease. This is the first time that a diagnosis of this condition has been confirmed during life, except by removal of the spleen.

On October 28, 1914, blood examination was as follows: Red blood corpuscles, 4,608,000; leucocytes, 6,480. Differential count: Polymorphonuclear leucocytes, 77%; mononuclear leucocytes, 21%; transitionals, 1%. The reduction in the number of leucocytes seemed to be directly due to the effect of the radium. There was, however, no marked change in the patient's condition. The temperature remained elevated. On November 1, a second treatment with radium was given. This was followed by a further fall in the leucocytes to 5560 per c. mm. Following this second radium application the patient became stuporous and toxic. Internal strabismus developed with nystagmus. The leucocytes were further reduced, on November 12, to 4980, and on December 2, to 2360. At this time the differential count showed: Polymorphonuclears, 37%; small mononuclears, 39%; large mononuclears, 19%; transitionals, 1%; myelocytes, 3%. The spleen seemed somewhat diminished in size, being felt 1½ inches below the costal margin. There was no improvement, however, and the child gradually became weaker and took her food badly.

Examination of the eyes by Dr. Powers showed the following interesting condition: Both fundi were pale, the region of the disk in each eye was white with no distinct margin. In the region of each macula there was a bright red spot, slightly larger in the left than in the right eye.

The patient continued to lose strength and died from exhaustion on December 24, 1914.

AUTOPSY.—The body is that of a greatly emaciated, white female infant, 61 cm. in length. The conjunctive and buccal mucous membrane are pale. The ribs and other bony structures of the body are very prominent. The abdomen is greatly distended. The lower edge of the liver and spleen can readily be seen through the abdominal wall. The abdominal muscles are very thin and there is practically no subcutaneous fat.

The pleural and pericardial cavities are not implicated.

The *thymus* on section presents the same characteristic appearance as seen in the lymph glands (see below).

The *heart* weighs 25 gm. The myocardium is reddish-brown, mottled with wavy yellowish-gray streaks.

The *lungs* are of a similar appearance. They are voluminous, contain air, have a delicate, smooth pleura and a pronounced lobulation. The lobules are separated by narrow, bluish-white, translucent lines, bordered on each side by a zone which is still more translucent. The center of the lobule forms the air-containing portion of the lung and is yellowish-pink.

The *spleen* is much enlarged. It weighs 100 gm. and measures 10 x 6 x 3.5 cm. Its capsule is delicate with a smooth and glistening surface. The consistence of the organ is increased and its edges are round. The parenchyma is mottled; small grayish and bright red areas about 2 mm. in size alternate with larger, patchy, yellowish-pink, frothy areas. On section the characteristic mottled appearance is more pronounced. The trabeculae and the Malpighian bodies are inconspicuous. The frothy, yellowish, slightly sticky material encountered on sections of the liver occurs here also.

The *stomach, duodenum and pancreas* appear normal.

The *liver* is greatly enlarged. It weighs 420 gm. and measures 28 x 10 x 4.5 cm. It is of normal shape. The capsule is delicate and its surface is smooth and glistening. Through it a uniform yellowish-pink, opaque parenchyma is visible. The lobules can be made out as tiny pink spots surrounded by a yellow periphery. On sectioning, the knife adheres slightly and a frothy, yellowish, slightly sticky material can be scraped off. The parenchyma is putty-like in appearance and consistence. The cut surface is similar in appearance to the external surface. The gall-bladder contains a small amount of apparently normal bile. The bile-ducts present nothing abnormal.

The *adrenals* are enlarged. They weigh 8 gm. and measure 4 x 3.5 x 1 cm. Their appearance externally presents nothing of interest. On section the medulla is more yellow than usual.

Kidneys.—The cortex of the kidneys is slightly swollen and has a yellowish tint. The glomeruli and striæ are in places indistinct. The *pelvic organs* appear to be normal.

Intestines.—The Peyer's patches of the small intestine, especially near the ileo-cæcal valve, are enlarged. The lymph follicles are very translucent. Just near the ileo-cæcal valve the mucous membrane of the cæcum is congested. The rest of the cæcum and the large intestine present large, translucent, solitary follicles.

Lymph Glands.—All the lymph glands are similarly involved. They are enlarged, discrete and slightly firm. Externally and on section they have a uniform, frothy, yellowish-pink color. The glands about the pancreas and hilus of the liver are most involved. The posterior cervicals on the right side are somewhat different from the glands of other regions. They are enlarged, more juicy, and both externally and on section they have a more reddish-pink color.

The *aorta* is normal in appearance.

The *bone-marrow* is hyperplastic and of a yellow color.

Brain, Spinal Cord, etc.—In the pia-arachnoid of the frontal lobe is a small amount of translucent, gelatinous material; otherwise the brain and spinal cord show nothing abnormal.

The following additional tissues were removed for microscopical examination—in gross they presented nothing abnormal: the thyroid, submaxillary, salivary glands, hypophysis, various cranial and peripheral nerves, skin, striated muscle, various arteries and veins.

MICROSCOPICAL FINDINGS.—The microscopical findings in this case closely resemble those of Case I; a detailed description will therefore be omitted, and emphasis placed upon additional findings.

Lungs.—The lung tissue throughout presents a picture similar to that described in the right lower lobe of the first case. Many of the bronchi, arteries and veins contain a few large cells, identical in appearance with those found in the air spaces.

Spleen.—The characteristic large cell in this case is also found in the lumina of the arteries.

Pancreas.—Both the acinar and island cells appear slightly swollen and granular. They frequently contain vacuoles of varying size and shape.

Liver.—The cells of the first type in places show an imperfect trabecular formation and are undoubtedly to be considered as altered parenchymatous cells. Cells of the second type are also found in the intima and in the lumina of the portal vessels.

Adrenals.—The medulla shows the same changes as in the first case. It is rather difficult to determine exactly where the medulla begins and the cortex begins. This makes the medulla look unusually wide. In the adventitia of a large artery of the capsule there is a mass of the characteristic large cells. In other parts of the capsule masses of what appear to be young cells of the same type occur. They are smaller and have a darker pink cytoplasm, which is more granular and does not contain so many small, clear droplets. Many of these cells contain red blood cells. Cells representing all stages from this apparently young cell, which closely resembles the polyblast of connective tissue, to the typical large cell are seen in these masses of cells and also scattered in the spaces of the capsule.

Kidneys.—The characteristic large cell is frequently seen in the glomerular tufts, between the tubules and at times in the capillaries.

Gastro-intestinal Tract.—The parietal and cuboidal cells of the gastric tubules contain small vacuoles. A few of the characteristic large cells are seen scattered in the lower part of the mucous membrane. The tubular epithelium of the colon contains some small vacuoles, which are to be differentiated from those of the large goblet cells.

Thymus.—Most of the lymphoid cells, of both the cortex and the medulla, have been replaced by more or less closely grouped large cells similar to those in the first case. Only a few imperfect lymphoid cells remain, and a sharp differentiation into cortex and medulla cannot be made.

Lymph Glands.—Glands taken from different regions of the body show an extensive replacement of the lymphocytes by a large cell, identical in appearance to that in the thymus. These cells are chiefly located in the medulla. In some glands the "Keimcentra" are very prominent and mitotic figures are frequent among the large lymphocytes within them. They also contain scattered large cells which closely resemble the characteristic large cell of the medulla, except that they contain nuclear fragments and red blood cells. These phagocytes are limited almost entirely to the "Keimcentra." There are no well-defined transitions between the proliferating large lymphocytes and the large, pale cells. Some of the large, pale cells are more or less filled with small, greenish-yellow pigment granules, especially in those areas where there is considerable congestion and hemorrhage. There is some patchy increase in young connective tissue. The endothelial cells of the vessels and sinuses are swollen, but there is no evidence of proliferation. The glands of the peritoneal cavity are more involved than the superficial glands.

Bone-marrow.—The fat is entirely absent and a large cell identical in appearance with the one in the spleen is present in large numbers.

Thyroid.—The acinar epithelial cells are swollen and project into the lumina as round or oval cells with a pale cytoplasm filled with droplets.

Submaxillary Glands.—The epithelium of the ducts and acini contains vacuoles.

Brain.—Scattered through the pia and the brain substance of both the cerebrum and the cerebellum are large cells, identical in appearance with the characteristic large cell of the spleen of the first case. These cells are most common in the neighborhood of the Purkinje cells. The greater part of the cytoplasm of the Purkinje cells is filled with small droplets, only a small zone of normal cytoplasm remaining about the nucleus. The cytoplasm of these cells resemble closely that of the characteristic cell mentioned above. The hypophysis shows no lesions.

Spinal Cord.—The anterior horn nerve cells have their cytoplasm filled with clear droplets. In the spinal root ganglia the bipolar cells have a pale nucleus and their cytoplasm is filled with small, clear droplets.

Nerves.—Nerves of various size and from various parts of the body show a vacuolization of their medullary sheaths.

The skin, striated muscle, arteries and veins of all sizes, and tonsils show no lesions.

DISCUSSION.—The origin of the characteristic large pale cells is not very clear. In structure, position and staining reactions they are identical with those described in the small group of cases of primary splenomegaly first reported by Gaucher, who at first considered them to be epitheliomatous cells; but at present this neoplastic theory has very little support. Some authors hold that they are endothelial cells, others that they are derived from the cells of the reticulum, and still others believe that they come from both. Recently, one author, Mandelbaum, has advanced the theory that they are derived from large lymphocytes.

In the present cases there is no evidence that the large cells are derived from any one particular tissue cell. On the other hand, there is good reason to believe that several different tissues may produce the same large pale cell. In some places there is strong evidence that they are derived from the endothelial cells of the lymph sinuses (Figs. 8, 10, 11). On the other hand, there are just as good reasons for believing that they arise from the cells of the reticulum (Figs. 2, 3, 4). In many areas the endothelium shows no change, while the reticular spaces are filled with large pale cells, many of which are closely related to the reticular fibers. This is particularly true of the spleen, where there is generally little change in the sinusoids, in marked contrast to the presence of the columns and clusters of large pale cells outside the sinuses. In some places small vacuoles were present in the cytoplasm of the large lymphocytes, and it is possible that some may develop into the large, pale granular cells; but no such transition was seen. In the liver the large, pale granular or vacuolated cells are most probably transformed hepatic cells. In certain places they are arranged in radiating columns. In some sections a crescent-shaped mass of finely granular, deep eosin-staining cytoplasm could be seen at one side of a large cell, suggesting a hepatic cell in which a small part of the normal cytoplasm had persisted, while the greater part had been changed by an infiltration of some homogeneous substance and the nucleus had become smaller. No normal hepatic cells were seen and, in this respect, the liver is identical with that in Niemann's case. Similarly, the young connective-tissue cells and fibroblasts may take up this lipid substance and become transformed into some of these large pale cells, thus accounting for the appearance of the latter about small arterioles (Fig. 18), and of those embedded in the periportal fibrous tissue of the liver. The large cells in the glomeruli of the kidney may come either from endothelial cells or from reticular cells. At no place is there evidence of any neoplastic nature in them. A few mitotic figures were seen in some of the endothelial cells, but only in those attached to the vessel wall. The large cells were not seen free in the large vessels. It is primarily the endothelial cells lining the small lymph sinuses and the cells of the reticulum that become transformed into these characteristic

large vacuolated cells, and of these (in our cases) the reticular cells of the lymphadenoid tissue seem the most susceptible.

The disappearance of the substance within the large pale cells on treatment with absolute alcohol or ether, and its atypical fat-like reactions to the microchemical tests for fats and lipoids, leave very little doubt but that the large cells owe their size to the accumulation, whether it be degenerative or infiltrative, of a lipid substance, the exact nature of which is unknown. This substance does not behave like fat; yet its reactions to neutral fat stains show that it is closely related to the fats. It resembles myelin. Apparently, it represents a lipid substance arising from a perverted metabolism. The nature and mode of formation of this lipid substance are obscure, but it is probably closely related to lecithin. Whether its accumulation in the large pale cells and in the parenchymal cells is due to a degenerative or to an infiltrative process cannot be determined with our present knowledge of the condition. The peculiar bilateral change in the medulla of the adrenal glands may play a very important rôle in this metabolic disturbance, resulting in the accumulation of the lipid substance in all of the tissues, liver, heart, kidney, pancreas and connective tissue, apparently wherever fatty degeneration and deposits occur. In fact, there is considerable fatty degeneration either superimposed on this "lipoid metamorphosis" or representing an end-product of it. It may also be, as Schultze first suggested, that the spleen, which is said to play a not unimportant part in fat metabolism in some abnormal conditions, is largely responsible in these cases.

The names applied to this disease are innumerable and misleading, because they attempt to be descriptive terms. They fail to describe the new cases and the constant variations which are being added each year, and which should all be included in a term which would connote the causal factor. As this, however, is unknown at the present time, considerable confusion would be avoided if all cases were termed simply "Gaucher's disease," until more definite information concerning the nature of the process is obtained. As the process in this disease is a very general one and not specific for the spleen, the term "splenomegaly" is a misnomer. As more cases are described, a greater or less number of organs seem to be involved. At first it was thought that only the spleen and lymph glands were involved, but the liver was then added, and, more recently, the thymus and the bone-marrow. In our cases the medulla of the adrenal glands must also be added to this list, and it is to be noted that similar but less prominent changes were found in other organs and in the central nervous system. It is also very probable that the case described by Schultze, in which there was implication of the spleen alone, associated with a lipoidæmia, represents an earlier stage in the same process, inasmuch as the morphology, position and microchemical reaction of the cells were similar. Schultze showed that the sections of the spleen of his case reacted to the microchemical tests for fats and lipoids just as did the sections of the generally accepted cases of Gaucher's disease described by Risel and by Schlagenhauser; and the same reactions were obtained in our case. Apparently, any

disease in which the spleen, together with any other organ, shows numerous large, pale granular or finely vacuolated cells, giving the characteristic microchemical reactions for lipoids and showing a tendency to be widely and diffusely distributed, belongs to this group, and any attempt to limit the condition to any single organ or any single set of organs is largely arbitrary.

Accordingly, it would appear that Gaucher's disease is not primarily a disease of the spleen or of any other organ or set of organs, but is a generalized process due to a disturbance in fat metabolism, manifesting itself by lipid metamorphosis, that is, by the more or less diffuse accumulation of lipid material in many cells with the formation of characteristic large pale cells. This process is most prominent in the hematopoietic system, especially in the spleen and lymph nodes, organs that are said to play a not unimportant rôle in abnormal fat metabolism.

SUMMARY.—It is quite evident that the characteristic lesion in these two cases is the widely diffused accumulation and proliferation of the large, pale granular or finely vacuolated cells, most prominent in the lymphadenoid tissues, but apparently involving more or less extensively the reticular cells and the lymph-vascular endothelial cells, the process being generally associated with localized accumulations such as have been described in the medulla of both adrenal glands. The process was equally marked in the lymph nodes as in the spleen and probably had begun simultaneously in both locations, other susceptible tissues being subsequently implicated. The large pale cell was also found in bronchi, arteries, veins, capillaries, glomerular tufts, scattered between renal tubules, in the mucous membrane of the stomach, in the capsules of various organs, in the pia, brain and in large numbers in the bone-marrow. The occurrence of vacuoles in the parenchymal cells of most of the viscera—including the heart, pancreas, kidneys—thyroid, submaxillary salivary glands, in the Purkinje cells of the brain, in the nerve cells of the anterior horn of the spinal cord, in the bipolar cells of the posterior root ganglion of the spinal cord, taken in conjunction with the negative results after the use of fat stains, indicates either a vacuolar degeneration or an accumulation of lipid material in those cells as in the large pale cells, and suggests the presence of a very general pathological process, involving especially the lymphatic system. The phagocytosis was more marked and extensive in the second case than in the first. There was also more fibrinosis, a greater proliferation of lymphocytes and more blood pigment than in the first case.

CONCLUSION.—The characteristic large, pale granular or finely vacuolated cell with its lipid contents, the predominance of this cell in all of the organs of the hematopoietic system, the familial character of the two cases, the clinical history, the physical and pathological findings, leave no doubt but that they belong in the group of cases first described by Gaucher. It is true that our cases showed a unique implication of the medulla of the adrenal glands, that the Peyer's patches and the thymus were equally involved and that there was a much more general and diffuse distribution of the character-

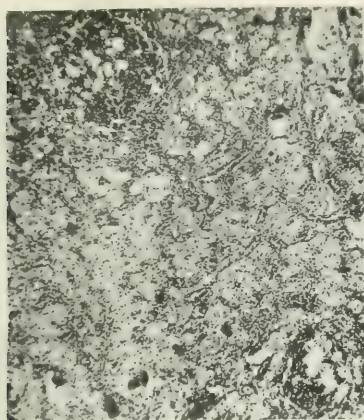


FIG. 1.

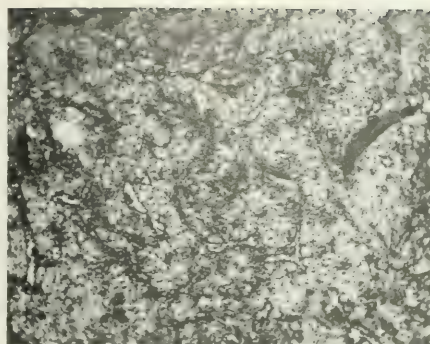


FIG. 2.

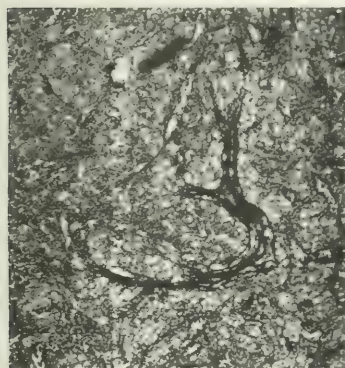


FIG. 3.

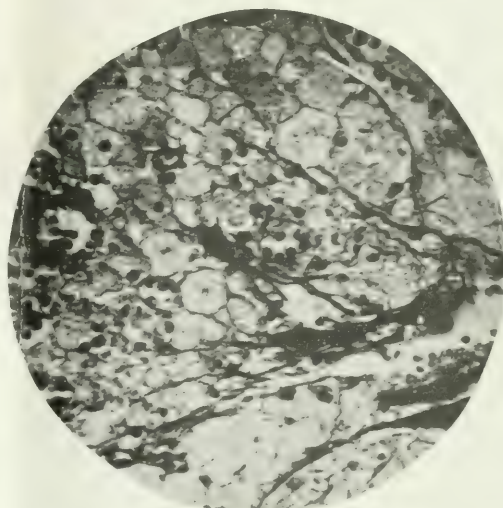


FIG. 4.

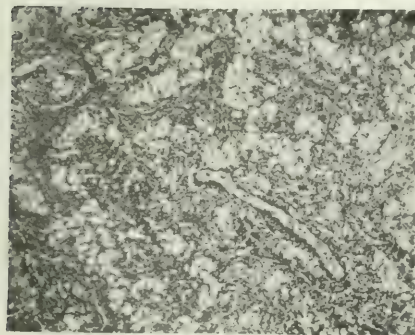
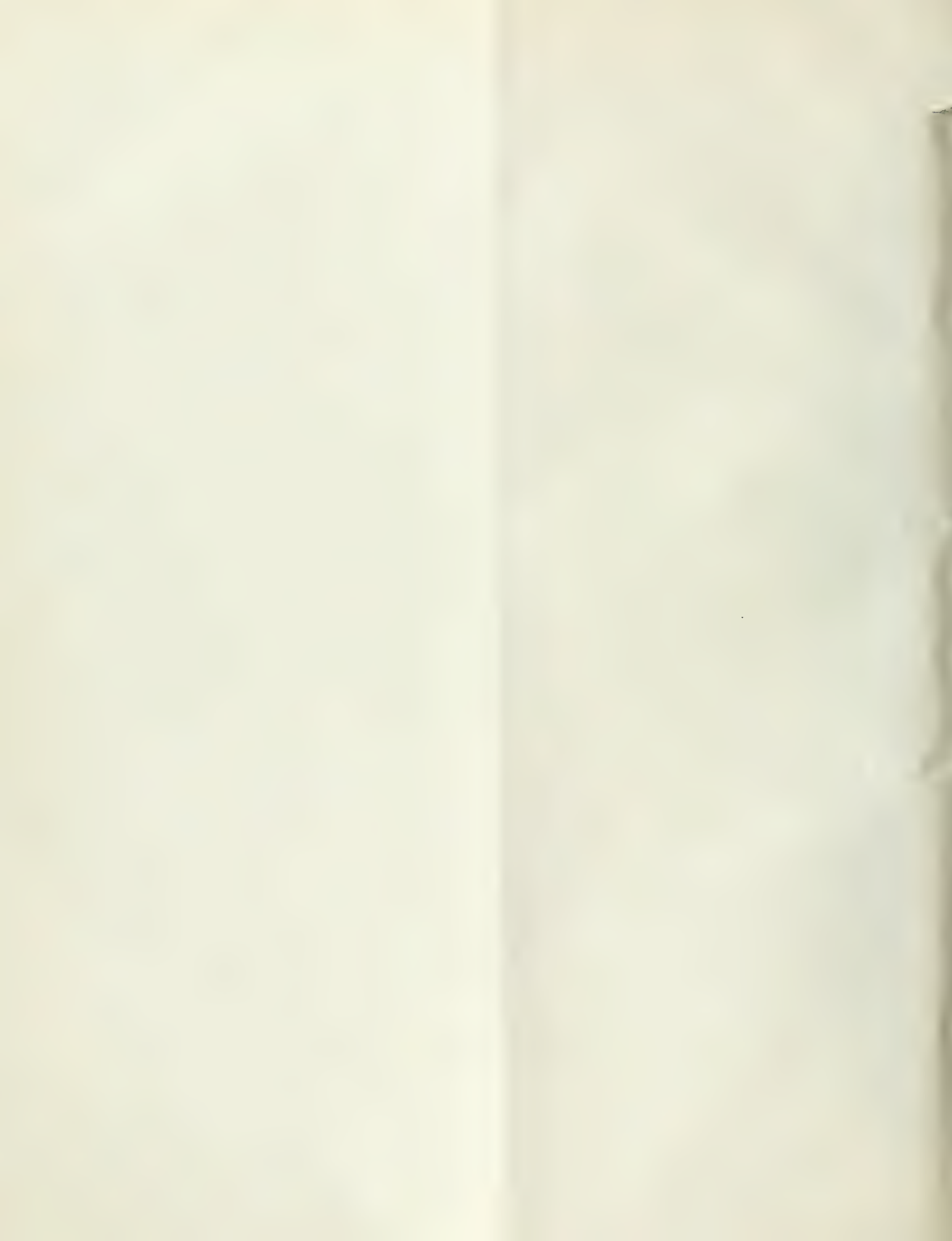


FIG. 5.



FIG. 6.



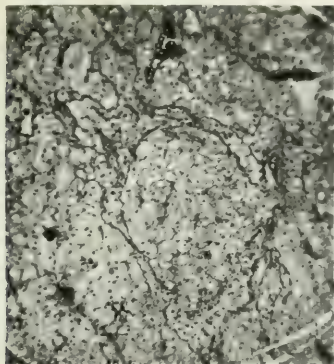


FIG. 7.

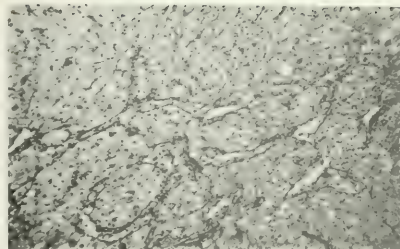


FIG. 8.

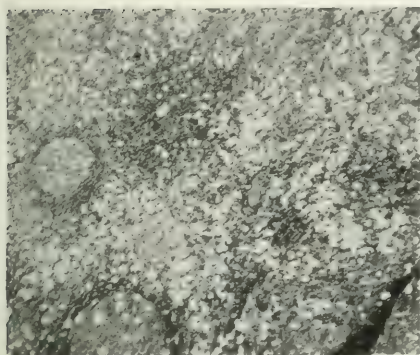


FIG. 9.

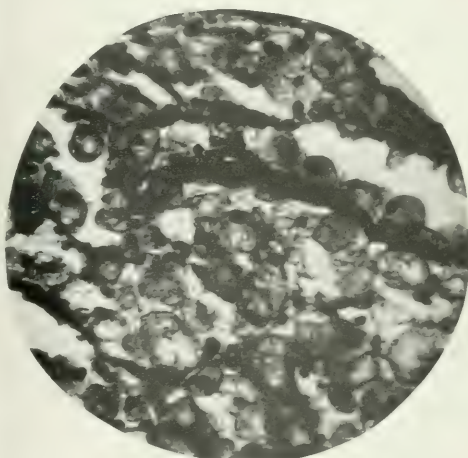


FIG. 10.

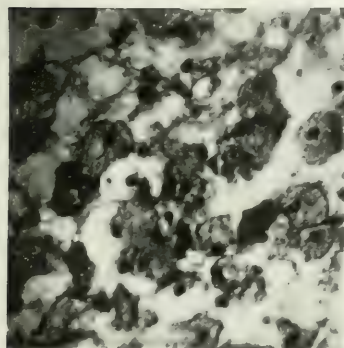


FIG. 11.

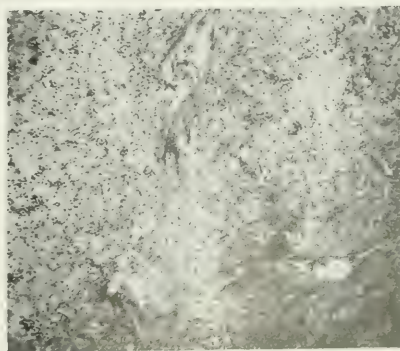
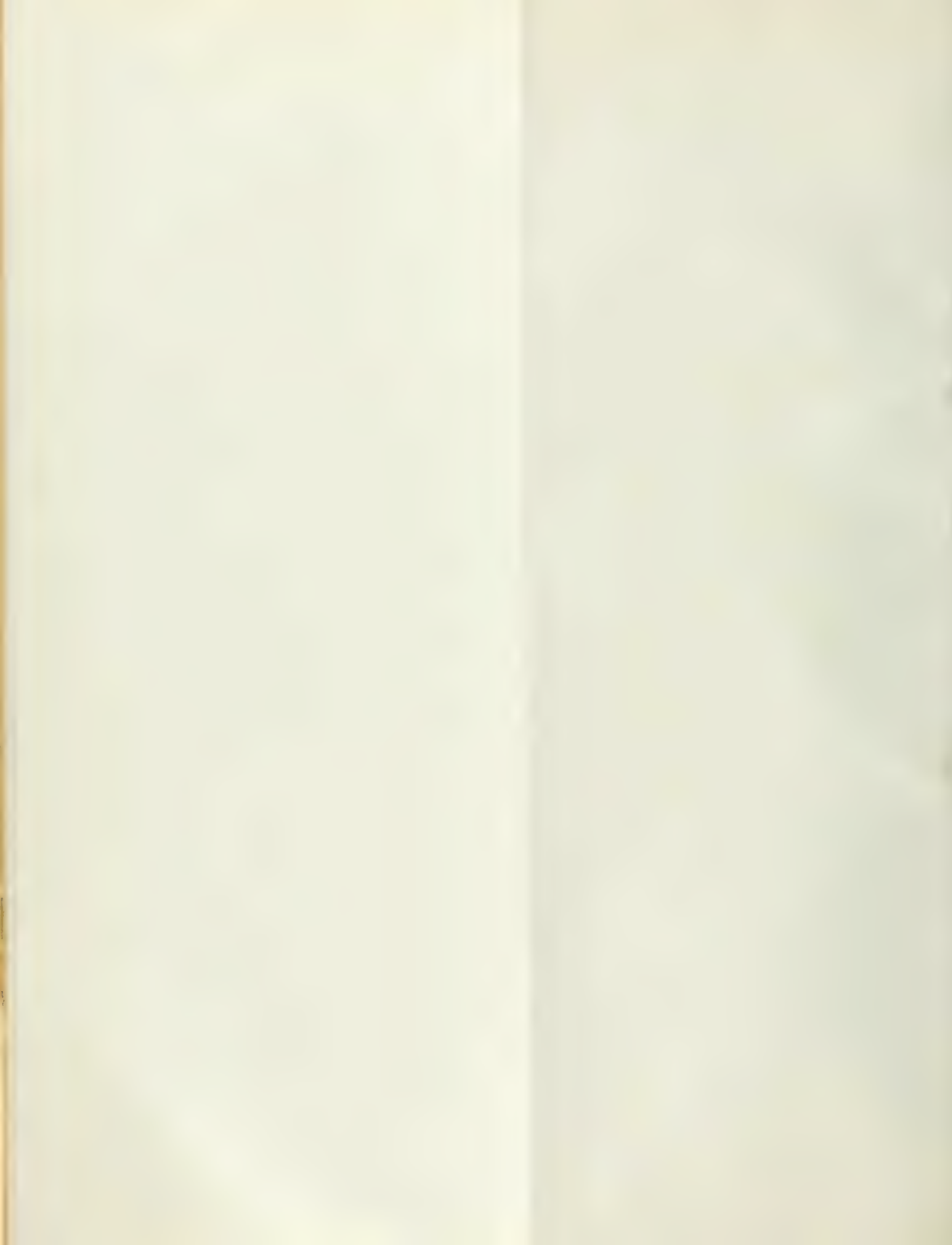


FIG. 12.



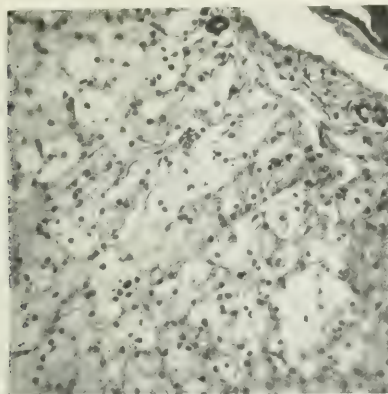


FIG. 13.

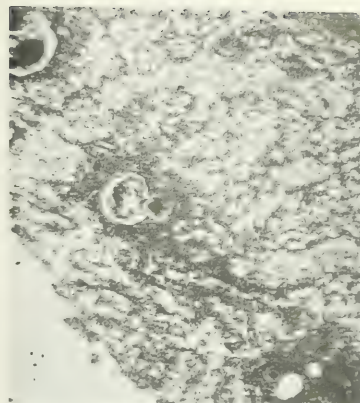


FIG. 14.

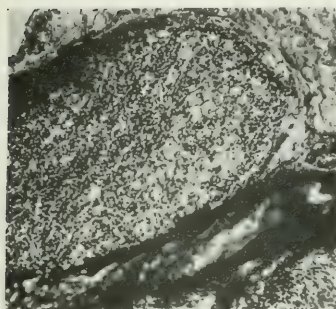


FIG. 15.

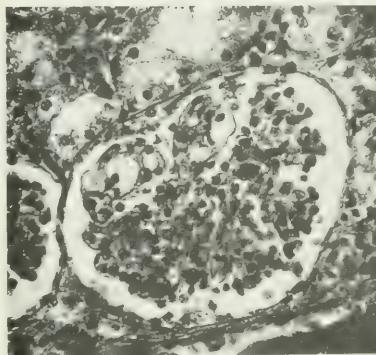


FIG. 16.

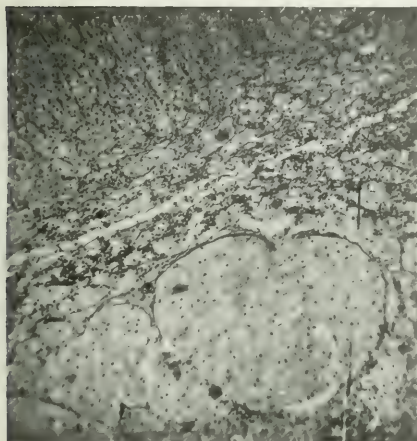


FIG. 17.

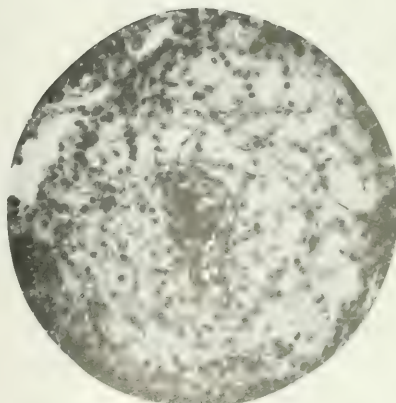


FIG. 18.

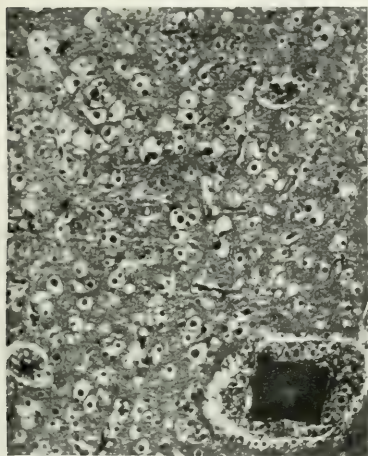


FIG. 19.

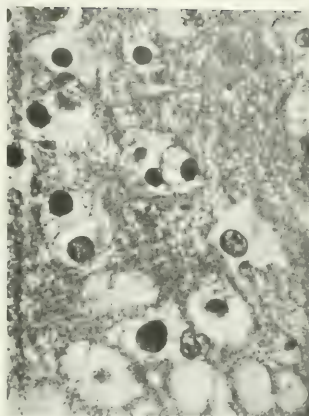


FIG. 20.



FIG. 21.

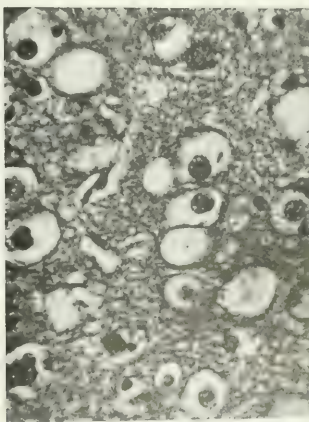


FIG. 22.

istic large cells; but this may be a manifestation of one and the same process, which in infancy is apt to be more rapid and widespread, as has been suggested by Niemann (see table).

FINAL SUMMARY.—In this report we have presented the cases of two infants, sisters, who did not thrive from birth and died, one at 11 months, the other at 15 months of age, from gradually increasing weakness. The most striking clinical feature was the great enlargement of the spleen and liver. The blood picture was that of a moderate anemia. The leucocytes were rarely increased, and for the most part were markedly reduced in number. The skin in both cases had a peculiar yellowish-brown hue, more marked on the face and exposed surfaces. In one case the diagnosis was confirmed during life by the examination of an excised lymph gland. Microscopically, in both cases nearly all the organs were found to contain large, pale, granular or finely vacuolated cells, in which there was a peculiar refractive substance having the chemical and staining properties of lipid material. These cells are apparently identical with those described by Gaucher, and later by a number of observers, in the condition called "Gaucher's disease." Our own cases and that of Niemann are the only ones in which the disease has been reported in infancy. The observation of cherry-red spots in the maculae of Case II, in view of the presence of similar cells in the nervous tissues of cases of amaurotic family idiocy (Figs. 21, 22), lends additional interest and suggests the possibility that the essential degeneration in the latter condition may be of a similar character.

DESCRIPTION OF PLATES.

FIG. 1.—Spleen (× 65). Iron hematoxylin stain. Shows the relative disappearance of the lymphoid cells in the pulp and the presence of many pale granular or vacuolated cells between the sinusoids. Note the similar large, pale cells within the Malpighian bodies, also the prominence of the endothelial cells of the sinusoids.

FIG. 2.—Spleen (× 70). Iron hematoxylin stain. Shows the distended sinusoids separated by columns and nests of large, pale, granular cells. This represents a typical section of the splenic pulp.

FIG. 3.—Spleen (× 65). Bielschowsky silver method for demonstration of the reticulum. Shows the general architecture of the spleen with the well-marked sinusoids, the intervening large, pale cells and their intimate relation to the reticulum.

FIG. 4.—Spleen (× 480). Bielschowsky stain. Shows the character of the large, pale cells and their intimate relation to the reticular fibers.

FIG. 5.—Lymph Gland from Case I (× 70). Hematoxylin and eosin stain. Shows columns and nests of large, pale cells imbedded in the lymphadenoid tissue. Compare with Fig. 9.

FIG. 6.—Lymph Gland (× 70). Hematoxylin and eosin stain. Shows in one portion the large cells just appearing; in another the complete replacement of lymphoid elements by the same.

FIG. 7.—Lymph Gland (× 65). Iron hematoxylin stain. Shows the complete replacement of the lymphoid cells by the large, pale, finely vacuolated cells which are enclosed in the reticular spaces.

FIG. 8.—Lymph Gland (× 70). Iron hematoxylin stain. Shows the large, pale cells apparently arising from the endothelial cells lining the sinusoids.

FIG. 9.—Lymph Gland from Case II (× 65). Hematoxylin and eosin stain. Shows the presence of the large vacuolated cells in

clusters and isolated in the lymphadenoid tissue. Note the presence of these cells in the germinal follicles, some showing phagocytosis.

FIG. 10.—Lymph Gland (× 480). Iron hematoxylin and eosin stain. Shows the character and location of the large, pale cells. Some of these cells are still attached to the wall of the sinus.

FIG. 11.—Lymph Gland (× 480). Iron hematoxylin and Van Gieson's stain. Shows the ragged, irregular outline of some of the large cells, the extension of their protoplasmic processes into the reticulum and the apparent origin of some of the cells from the reticulum.

FIG. 12.—Liver (× 70). Iron hematoxylin stain. Shows the fibrosis, the distortion of the intralobular architecture, and the absence of normal hepatic cells.

FIG. 13.—Liver (× 260). Iron hematoxylin stain. Shows the character of the parenchymal cells. Note the pale and the finely vacuolated darker types, also the absence of normal liver cells.

FIG. 14.—Thymus (× 80). Iron hematoxylin stain. Shows three Hassall's corpuscles, each surrounded by a zone of lymphocytes and columns and nests of large, pale, granular cells.

FIG. 15.—Lymph Follicle in Intestinal Submucosa (× 90). Hematoxylin and eosin stain. Shows the presence of the large, finely vacuolated cells to one side of the lymphoid mass.

FIG. 16.—Kidney (× 370). Iron hematoxylin stain. Shows a glomerulus. Note the characteristic large, pale, granular cells in the capillary tuft.

FIG. 17.—Adrenal (× 80). Iron hematoxylin stain. Shows the inner portion of the cortex and part of the medulla. Note the large masses of pale, granular cells inclosed in the reticular spaces of the medulla, the smaller, more scattered foci and the numerous red blood cells (stained black).

FIG. 18.—Wall of a Small Blood-vessel in the Lung (× 340). Hematoxylin and eosin stain. Shows a zone of characteristic large, pale, granular cells surrounding the wall of the vessel.

FIG. 19.—Brain (× 160). Iron hematoxylin and eosin stain. Shows the cortex of the cerebrum with the characteristic large, pale, granular cells. Note the apparent origin of these cells from the vessel endothelium.

FIG. 20.—Brain (× 450). Iron hematoxylin and eosin stain. Shows the cortex of the cerebrum with the characteristic large, pale, granular cells.

FIG. 21.—Brain of Amaurotic Family Idiocy (× 160). Hematoxylin and eosin stain. Shows the cortex of the cerebrum with large, pale, granular cells. Note the close resemblance of these to the cells in Fig. 19.

FIG. 22.—Brain of Amaurotic Family Idiocy (× 450). Hematoxylin and eosin stain. Shows a portion of the cortex of the cerebrum with the large, pale, granular cells. Note their close resemblance to the cells in Fig. 20.

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PLEURAL EOSINOPHILIA. WITH REPORT OF A CASE.

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INCIDENCE.

Eosinophile pleural effusions have been recorded in 68 cases. Sixty-three of these have been assembled and analyzed by E. Schwarz¹ in his recent monograph on the general subject of eosinophilia. In addition to these, cases have been reported by Baur,² Kipp,³ and Mosny and Portocalis.⁴ These instances of the presence of eosinophile cells in pleural effusions are few indeed in comparison with the great number of effusions which have been examined during the 15 years that have passed since Widal and Ravaut⁵ called attention to the clinical significance of pleural cytology. This figure, however, cannot be taken to indicate the actual incidence of pleural eosinophilia. It may be assumed with certainty that many

pleural fluids have not been examined microscopically, and that relatively few of them have been stained with polychrome dyes, proper for the demonstration of eosinophiles. The case to be reported almost escaped recognition because of a temporary failure to apply an eosin-containing stain, and it serves as a text for calling attention to the knowledge which will be gained by the use of polychrome stains in the routine study of pleural effusions. Pleural eosinophilia, nevertheless, is a comparatively rare condition. Its incidence, as determined by investigators applying constant methods to cases in series, is about 1 to 5 per cent of all cases of pleural effusion.

Pleural eosinophilia following lobar pneumonia, as in the instance which is the subject of this communication, has been

TABLE I.
SUMMARY OF CASES OF POSTPNEUMONIC PLEURAL EOSINOPHILIA.

Author.	Etiology.	Day of puncture.	Red blood cor.	% Eosinophiles.	% Poly-neutro.	% Lymphocytes.	% Endothelial.	Remarks.
Barjon & Cade. ⁶	Postpneum.	21, 26	Numerous.	46, 46	22, 11	16, 5	15, 10	Animal inoculation negative.
Sandomirsky. ⁷	"	24, 27	20, 13	69, 24	9, 54	
Widal & Faure-Beaulieu. ⁸	"	3, 5, 9, 10 19, 22, 26 31, 34, 56, 69	3900, 2700 730, 1960	60, 52, 65, 24 72, 82, 85, 76 2	10, 8, 1, 1, 9 0, 5, 1, 5 2, 5, 7	3, 6, 6, 4 1, 1, 8, 1 2, 71	23, 31, 18, 16 21, 12, 7 7, 17, 18	Some mast-cells. Enormous toxicity. Eosinophiles in blood, 3% to 16% to 0.1%.
Malloizel. ⁹								
Obs. XLV.	"	9, 15, 18	Present.	A few at first, then many, then none.	Scanty.	
Obs. XLVI.	"	1, 8	"	"	Abundant.	
Obs. XLVII.	"	8, 11, 22	Fluid at first purulent; then hemorrhagic.	None at first, then many.	Many.	Few.	
Obs. XLVIII.	"	1 month.	Many.	Many.	None.	Many.	Not tuberculous.
Mosny, Dumont, & Saint-Girons. ⁴	"	6, 7, 9 11, 13, 16 18, 21, 23 25, 27	0, 3, 4 28, 20, 51 74, 85, 81 78, 5, 86	73, 80, 15 56, 14, 7, 10 11, 1, 3, 1, 5 0, 5, 0, 5	1, 5, 0, 27, 15 12, 6, 27 1, 0, 0, 5 0, 0	25, 20, 58 26, 70, 56 39, 30, 14, 7 6, 5, 10, 8	Fluid (1) purulent. (2) Sero-purulent. Sterile, with 11% mast-cells. Blood, 2.5-11% eosinophiles.

recorded in eight cases. Of the 68 cases mentioned in the preceding paragraph, eight were of metapneumonic occurrence, giving approximately 12 per cent as the special incidence of postpneumonic pleural eosinophilia among all eosinophilic pleural effusions. The findings in these cases are shown in Table I.

REPORT OF CASE.

J. A. N., white, male, aged 30 (Gen. No. 101461, Medical No. 33908), was admitted to The Johns Hopkins Hospital on March 20, 1915, to the medical service of Dr. T. C. Janeway.

The patient was a sailor whose health had always been robust. Since the age of 16, he had lived on ship-board, sailing frequently in the tropics. He had never suffered from any severe acute illness and had not acquired any tropical disease. Gonorrhea eight years previously and periodic excesses in drinking alcohol were the only other significant facts in his past history.

He complained of "pain all over, sick stomach, and spitting blood." The history of the illness which caused him to come to the hospital was a typical account of the onset of a lobar pneumonia. When he entered, on the fourth day of his illness, he had consolidation of the entire right lung. His temperature was 105° F.; respirations 40 per minute. The results of the special examinations were as follows:

Blood: (March 20th) R. B. C. 5,032,000. Hb. 85 per cent. W. B. C. 11,000. The differential count, with Wilson's stain, showed polymorphonuclear neutrophils 93 per cent; mononuclears 7 per cent. No eosinophiles were seen in counting 250 cells. The blood culture was negative, but a culture from material obtained by puncture of the lower lobe of the right lung yielded a pneumococcus of Group II. A similar pneumococcus was grown in pure culture from the sputum. The Wassermann test was negative. Chlorides were absent from the urine. No tubercle bacilli were found in the sputum. The feces were examined frequently for ova and parasites, but none were found.

The temperature remained between 103° and 105° F. until March 23d, the seventh day of the disease, after which it gradually declined. For the next seven days, however, the temperature remained between 99° and 100° F., with the pulse proportionately accelerated, while the respirations were from 20 to 25 per minute. During this time, the signs of resolution began to supersede those of consolidation. The leucocyte count, which had been 25,000 became 14,000 on March 27th. No eosinophiles had been seen in the differential counts up to this time. The percussion note remained dull at the right base; and as empyema was suspected, the pleural cavity was aspirated on March 29th.

Thoracentesis I.—Five hundred cubic centimeters of a cloudy, amber fluid were withdrawn. This fluid clotted readily and had a specific gravity of 1015; it contained 40 grams of protein and 2.5 grams of chlorides per liter. Cell count: White cells, 580 per cu. mm.; red corpuscles, 2000 per cu. mm. Sediment of this fluid stained with methylene blue showed that the predominant cell was the "small mononuclear." No bacteria were seen. Cultures of this fluid remained sterile, and a guinea-pig inoculated with a considerable amount of the sediment was not affected.

Within a week after the aspiration of the fluid, the patient's temperature became normal, and remained so. The signs of consolidation gradually disappeared over most of the right lung, except over a small area in the interscapular region, while the dullness at the right base persisted. A second aspiration of the right pleura was performed on April 5th.

Thoracentesis II.—Twenty cubic centimeters of turbid yellow fluid were obtained. This fluid clotted quickly. The white cells numbered 600 per cu. mm., showing a predominance of eosinophiles when stained with Wilson's stain. The differential count showed

a significant contrast with that of the blood, the leucocytes of which numbered 11,200 on the day of the aspiration.

Fluid.	Percentage in pleural fluid.	Percentage in blood.
Polymorphonuclear neutrophile	6	72
Polymorphonuclear basophile	0	5.6
Eosinophile		
Polymorphonuclear	44	1.2
Mononuclear	1	0
Small mononuclear	30	3.6
Large mononuclear	16	7.2
Transitional	2	4.4
Endothelial cells	1	0
Totals	100	100.00

Cultures and inoculations with this fluid were negative.

It became evident that the pleura was thickened over the right base, with little or no fluid remaining in the chest-cavity. A radiograph (Plate No. 29060), taken on April 16th, showed: "Mediastinitis. Extensive infiltration of both lungs. Patchy consolidation of the upper lobe of the right lung, with thickened pleura over this lung." It was the opinion of Dr. Baetjer that these changes were largely postpneumonic, and could not be called tubercular. Tuberculin tests (Calmette) were negative.

On April 10th, the right pleura was again tapped. At this time the blood showed W. B. C. 7500, with 15 per cent of eosinophiles.

Thoracentesis III.—Fifteen cubic centimeters of yellow turbid fluid, which clotted almost immediately. A sp. gr. determination and cell count were not made. The hydrogen-ion concentration of this fluid was 10-7.5 (Dr. Levy)—practically a neutral reaction. Differential count. Wilson's stain. 300 cells counted.

Type of cell.	Percent.
Polymorphonuclear neutrophile	5.6
Polymorphonuclear basophile	0.3
Eosinophile	
Polymorphonuclear	46.0
Mononuclear	1.0
Small mononuclear—granular	2.3
non-granular	39.0
Large mononuclear	1.6
Endothelial cells	1
Unclassified (degenerated cells)	3.2
	100.0

With Ehrlich's stain the differential count was:

P. M. N. 15 per cent.
P. M. E. 40 per cent.
S. M. 40 per cent.
L. M. 5 per cent.

SPECIAL STUDIES OF THE CELLS OF THE PLEURAL FLUID.

When treated with ammonium sulphide for the "iron-reaction" in the granules of the white cells, according to the method of Barker, smears showed that nearly all the coarsely granular cells exhibited dark brown to black granules. Forty per cent of the white cells gave this reaction—a percentage about equal to that of the eosinophiles present in the fluid.

Oxydase reaction: Smears treated with β -naphthol and dimethyl-paraphenylenediamin, and counter-stained with aqueous safranin, showed the violet-black granular oxydase reaction in 59 per cent of the white cells. Obviously, this included some of the mononuclear cells other than the mononuclear eosinophiles.

The patient improved steadily, the pulmonary signs gradually clearing. He was discharged on April 20, 1915.

On May 17th, he was seen when he landed from a cruise during which he had served as stoker on a steamship. He looked well and had gained weight. There was slight dullness at the right base, but no signs of pleural effusion. His leucocytes were 7900 per cu. mm., with only 1.5 per cent of eosinophiles, and a practically normal differential count. No mononuclear eosinophile cells were present in the blood at this or any other time.

DISCUSSION OF CASE.

This case presented two metapneumonic phenomena, namely: a pleural effusion and eosinophilia of the pleural fluid, together with blood-eosinophilia. The details of these conditions have been described with the report of the case; a discussion of their significance will be taken up in the succeeding paragraphs.

Small serofibrinous pleural effusions are common in pneumonia. Such effusions have been found in 65 per cent of a series of cases studied by puncturing the pleura.² Significant metapneumonic effusions, large enough to give physical signs (400 cc.), occur in 5 per cent of the cases.³ In this case, the exudate was straw-colored, with sp. gr. 1015, albumin 40 grams per liter, 600 white cells and 1000-2000 red cells per cu. mm. It clotted quickly. Its reaction was neutral, with an H-ion concentration of $10^{-7.5}$, which eliminates any chemical abnormality which may affect the staining reaction of the cells of the exudate. The fluid was non-toxic when injected into guinea-pigs, was sterile when cultured, and did not produce tuberculosis in the animals into which it was injected. Corroborative of the non-tuberculous nature of the exudate, was the fact that at the time of the removal of the fluid, the patient gave no reaction to the 1 per cent and 5 per cent tuberculin conjunctival tests. The cytology of these exudates is variable; usually the polymorphonuclear leucocyte is predominant; rarely, as in this case, the eosinophile is the chief cell.

Eosinophiles in the blood in lobar pneumonia are usually rare before the crisis, begin to appear shortly before or after the crisis, and rise to normal or increased numbers after the crisis. The noted cases of postcritical eosinophilia in pneumonia seem to indicate that the condition is partially independent of the local process and the fever, but that it is in some way associated with the reaction by which the organism regains health. It seems likely that some substance which stimulates the production of eosinophiles is produced in the diseased tissues. The eosinophiles in the blood in all these cases have been of the usual polymorphonuclear type of a-cell.

Pleural eosinophilia after pneumonia, which has been observed eight times, has always been associated with blood eosinophilia, but differs both in degree and in exact morphological type of the eosinophile cell which appears in the blood. The local eosinophilia may amount to from 40 to 80 per cent of the cells of the pleural exudate, while the blood-eosinophilia is generally of a lower degree, in this case 47 per cent for the former as compared with 15 per cent for the latter. In the absence of any other reason for eosinophilia, the hemic and pleural eosinophilia must be attributed to a common cause

associated with the specific disease—an eosinotactic substance, the nature of which will be considered later.

The eosinophiles in the pleural exudate were very different from those present in the blood. In addition to the usual multilobed eosinophile, this fluid contained mononuclear eosinophiles, whose characteristics are shown in the accompanying illustration (Fig. 1 (1)). These mononuclear eosinophiles varied in diameter from 11 to 15μ ; the nucleus was round, filling about one-half of the cell; it was dense, but not so dense as the nucleus of the lymphocyte, and contained masses of chromatin of varying size and shape. The cytoplasm was faintly basophilic and contained large refractile granules, which stained intensely red with eosin, gave the oxydase reaction, and showed a brown reduction of ammonium sulphide, when tested for the "iron-reaction," characteristic of eosinophiles. These cells looked like the typical eosinophilic myelocyte.

Two main theories of the origin and nature of these cells have been proposed. Ehrlich⁴ and his followers, applying their theory of the myelogenous origin of eosinophiles, regard these cells as emigrated blood-eosinophiles, which have assumed a mononuclear form in the process of karyorrhexis. Dominici⁵ and Widal⁶ have held the opinion that these eosinophiles arise locally in the diseased structure by myeloid metaplasia of lymphoid tissue. The occurrence of mononuclear eosinophiles in nasal polyps and numerous other pathological and experimental eosinophilic lesions, is strong evidence in favor of the supposition that they have a local origin. Schwarz⁷ sums up the controversy by saying that while the bone-marrow usually plays the chief rôle in the increase of the eosinophiles, the fixed mesenchymal cells may also give rise to them. In the embryo, hematopoietic mesenchyme is widely distributed. In the adult the bone-marrow becomes the chief seat of blood formation, but throughout the body myeloid rests remain in a state of latent function. This tissue, present in the spleen, lymph-nodes, intestines, and in the adventitia of blood-vessels, resumes its function when acted upon by the proper stimulus, *e. g.* an eosinotactic substance, and produces any or all of the myeloid cells.

Among the mononuclear cells of this fluid were a number of granular cells which could not be classed with either the ordinary lymphocyte or myelocyte. These cells gave typical oxydase reactions, and had characteristics suggesting a myeloid origin, similar to that proposed for the eosinophiles. The other elements of the mononuclear group (called by Kipp⁸ and Pappenheim "Group L"), were typical lymphocytes and endothelial cells.

Occasionally, small basophilic cells with "budding nuclei" were found. These were difficult to distinguish from normoblasts (Dr. W. Baetjer) when the origin of the specimen was not known. Such a cell is shown in Fig. 1 (8).

Basophilic leucocytes formed 0.3 per cent of the cells (Fig. 1 (7)). In 1913, Mosny and Portocalis⁹ found such basophiles in a pleural effusion and described their discovery as "un élément nouveau." They are probably mast-cells from the pleura, and have no special significance.

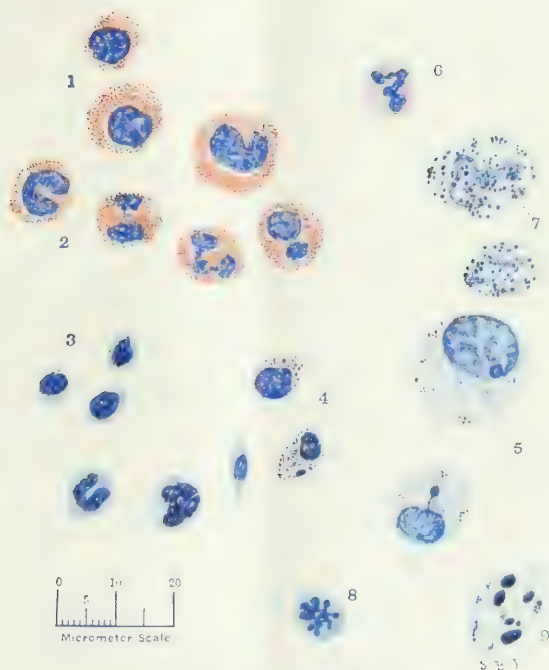


FIG. 1.—Cells of Pleural Fluid, Drawn to Scale with Camera Lucida. Wilson's Stain.

1. Eosinophiles—mononuclear.
2. Eosinophiles—polymorphonuclear.
3. Mononuclears—lymphocytes.
4. Mononuclears—with polychrome granules.
5. Mononuclears—endothelial cells.
6. Polymorphonuclear neutrophile.
7. Polymorphonuclear basophiles.
8. Mononuclear cell with budding nucleus.
9. Degenerated cell.

Polymorphonuclear eosinophiles formed 5.6 per cent of the cells of this exudate. They are without significance here, except as an indication of the absence of any very acute inflammation at the time of the aspiration of the pleura.

Occasionally, bizarre elements were found, large vacuolated cells containing polychromatophilic granules and masses of chromatin, which took a deep stain. There were evidently degenerated cells, showing a striking contrast to the fresh-looking mononuclear eosinophiles (Fig. 1 (9)).

ETIOLOGY.

The etiology of pleural eosinophilia has never been elucidated. The most positive inference deducible from the reports of the condition is that the substance determining the presence of eosinophile cells in effusions is a property of the exudate itself, and is independent of the bacterial, mechanical, or other cause of the effusion. Pleural eosinophilia has been found in pleurisy due to the following causes:¹ trauma, tuberculosis, sepsis, typhoid fever, syphilis, pleuropneumonia, pneumonia, polyarthritis, nephritis, pulmonary gangrene, hemorrhagic infarct of the lung, endothelioma, septic endocarditis, gonococcal sepsis, myocarditis, cardiac insufficiency, puerperal sepsis, neoplasm, influenza.

From this list of heterogeneous diseases involving the pleura which have been associated with eosinophilic exudates, no etiological conclusions can be drawn. The list, however, serves to show that the eosinotactic substance is independent of the local cause of the pleural effusion. Weidenreich¹¹ and others have considered that the erythrocytic content of the exudate determined the degree of the eosinophilia. In conclusive opposition to this may be taken the investigations by which it has been shown that eosinophilic granules have little in common with hemoglobin. Staëbli¹² has demonstrated that cells which actually ingest red corpuscles do not form eosinophile granules. If, however, Weidenreich's hypothesis had not been disproved, the fact that one-third of the exudates reported contained a minimal number of red blood-corpuscles would indicate the inadequacy of his explanation. In a similar manner, attempts to relate the eosinophilia to the presence of other cells in the exudate have been unsuccessful. The cytological formulæ of the exudates are too inconstant to serve as a basis for etiological deductions. The sterility of the exudate or its bacterial content has no influence upon the presence or absence of eosinophilia. As a rule, bacteria or their products tend, on the contrary, to exert an anti-eosinophilic action. Widal and Ravaut⁸ have shown that most of the eosinophilic exudates are sterile, but that some of them exhibit an unusual degree of toxicity for laboratory animals. The experiments on which these conclusions are based are negligible as regards their bearing on the question of toxicity, but they point in the direction in which is to be sought the substance which stimulates the production of this type of eosinophilia. Since all other factors have been eliminated, the chemical properties of the exudate appear as the important element in the reaction. Schwarz¹ has advanced the hypothesis that protein split products in the exudate form the eosinotactic substance which

produces the local or pleural eosinophilia (histoeosinophilia) together with its associated blood-eosinophilia (hemoeosinophilia). In an exudate undergoing resorption or, at least, becoming altered by the action of immune ferments, split products of proteins are formed, and these substances are demonstrable in the exudates as proteoses and peptones. The experimental work on anaphylactic eosinophilia and eosinophilia in helminthiasis has shown that the split products of proteins are capable of producing both local and general eosinophilia. As ferment action in any exudate, regardless of the immediate cause of the effusion, produces these eosinotactic bodies, this hypothesis is the only one broad enough to include all the known factors in the occurrence of pleural eosinophilia. The hypothesis, however, is only partially established by experiment, but it seems especially worthy of consideration, as it correlates a known mild process with a known biological healing-reaction, and as it explains how pleural eosinophilia may occur in many different forms of pleurisy.

DIAGNOSTIC SIGNIFICANCE.

The eosinophilia of pleural effusions occurs in so many diverse conditions that it cannot be correlated with any special morbid process. The small number of tuberculous pleurisy in the cases of pleural eosinophilia has been pointed out by several authors. For instance, Widal and Ravaut⁸ found one instance of eosinophilia in fifty tuberculous effusions. Aside from the suggestion afforded by this, that a pleural effusion containing eosinophiles is usually not tuberculous, no diagnostic significance can be attached to the presence of an eosinophile exudate.

PROGNOSTIC SIGNIFICANCE.

Eosinophile pleural effusions are generally transient and benign. The fatal ending in the lethal cases has been determined by such complications as septic endocarditis, rather than by the pleural or pulmonary disease. On the hypothesis that the eosinophilia is conditioned by the absorption of protein split products from an autolyzing exudate, the mildness of eosinophile effusions is comprehensible. The finding, therefore, permits the making of a favorable prognosis.

SUMMARY.

This communication presents the account of a case of post-pneumonic pleural effusion which contained 45 per cent of eosinophiles. The report of eight similar cases gathered from the literature are summarized.

Many of the eosinophile cells of this exudate were of the mononuclear type. The patient's blood exhibited a slight eosinophilia, but did not contain any mononuclear eosinophiles. The morphology of these pleural eosinophiles suggests strongly that they have a local origin outside of the bone-marrow.

A review of the possible etiological factors in pleural eosinophilia seems favorable to the hypothesis of Schwarz:¹ that protein split products in an exudate undergoing absorption

may constitute the eosinotactic substance that produces both the general eosinophilia and the local eosinophilia.

Eosinophilic exudates have no diagnostic significance, but are of good prognostic import.

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A COLORIMETRIC METHOD FOR THE DETERMINATION OF THE HYDROGEN ION CONCENTRATION OF BIOLOGICAL FLUIDS, WITH SPECIAL REFERENCE TO THE ADJUSTMENT OF BACTERIOLOGICAL CULTURE MEDIA.

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INTRODUCTION.

The continuation within the organism of certain physiological processes depends in great measure upon the character and the constancy of the reaction of the body fluids. Changes in either will be attended by serious consequences to the cells and enzymes which find the body fluids, and more especially the blood, their natural medium. The biological importance of the constancy of the reaction of the blood has been especially emphasized by the recent studies of Henderson (1). These have shown that there exists within the organism a regulatory mechanism whereby the normal reaction of the blood is permanently maintained.

Equally important is the reaction of the medium for the successful perpetuation of life outside of the organism. This is well illustrated by the well-known and intimate association between the acidity or alkalinity of solutions containing active enzymes and the rate of their activity, and also by the influence which the reaction of a bacteriological culture medium exerts upon the biological characters and the viability of bacteria. It is not unlikely, too, that the success or failure attending the cultivation of groups of cells or tissues *in vitro* depends, in no small measure, upon the reaction of the plasma; indeed, the frequent transfer of such tissues from media containing the products of their metabolism to fresh plasma prolongs their life. The proper adjustment of the reaction of a biological fluid is, therefore, of the greatest importance for the favorable progress of many physiological processes.

As will be shown later, an exact knowledge of the reaction of a medium can be gained only from a determination of its hy-

drogen ion concentration. It is the purpose of this paper to present a simple colorimetric method which makes it possible to determine with considerable accuracy and rapidity the hydrogen ion concentration of biological culture fluids, and to show how such media can be adjusted to any optimal concentration of ionized hydrogen.

THE REACTION OF A SOLUTION.

Recent progress in our knowledge of the physico-chemical properties of solutions has changed considerably our conception of the reaction of a solution. The importance attributed to indicators in ascertaining the reaction of a medium, and to their value in the readjustment of such a medium to the proper reaction by titration, is gradually dwindling before the extensive knowledge gained by modern physico-chemical studies. Indicators, as we now know, do not necessarily change color at the neutral point, but rather at a definite equilibrium of hydrogen and hydroxyl ions which is peculiar to each indicator, this point of change being dependent upon the chemical constitution of the indicator. It follows, therefore, that the determination of the reaction of a medium by titrating to a convenient end-point is without real significance.

According to the theory of solutions, the acidity in water is explained by the occurrence of hydrogen ions, formed from dissolved electrolytes, in excess of hydroxyl ions; neutrality is, therefore, the condition when, as in pure water, the two concentrations are equal. Because it is easier and more accurate to determine the hydrogen rather than the hydroxyl

ion concentration of a solution, it has become the established usage to express its reaction in terms of hydrogen ions.

PRESENT METHODS OF ADJUSTING THE REACTION OF CULTURE MEDIA.

In most bacteriological laboratories of this country adjustment in the reaction of culture media by titration has largely replaced all other methods. In a very recent paper Clark (2) has critically reviewed the method of "titratable acidity," and has set forth in a comprehensive way the reasons why the titrimetric method in its present form is inaccurate.

The inadequacy of the method of titration is attributable chiefly to the physico-chemical properties of the available indicators. The indicator most commonly employed for the titration of media is phenolphthalein which, like most indicators possesses no true end-point, since its zone of color change is broad, lying between the hydrogen ion concentration of $pH=8.00$ and $pH=10.00$.¹ If the tint of phenolphthalein at $pH=8.50$ is taken as a standard end point it is possible to show that media corrected from this point to definite degrees on the Fuller scale have different hydrogen ion concentrations.

This discrepancy can be demonstrated quite readily, if one chooses at random various samples of laboratory media and compares the titratable acidity with the actual hydrogen ion

TABLE I.

A COMPARISON BETWEEN THE DEGREES IN REACTION (FULLER SCALE) AND THE HYDROGEN ION CONCENTRATION OF VARIOUS MEDIA.

No.	Medium.	Degrees in Fuller Scale.	Hydrogen Ion Concentration. Value for pH .
1	Plain broth	+0.8	7.3
2	Plain broth	+0.4	7.8
3	Plain broth	+0.5	7.5
4	Plain broth	Neutral	8.4
5	Plain broth	+1.0	7.7
6	Veal-infusion	+1.0	7.1
7	Veal-infusion	+0.5	8.1
8	Veal-infusion	+0.9	7.6
9	Sugar-free broth	+0.9	7.5
10	Plain broth	+0.8	6.9
11	Liebig's broth	+0.5	7.9
12	Extract	+1.0	7.2
13	Ox-heart broth	+1.1	6.9
14	Liebig's broth	+0.8	6.9
15	Plain broth	+0.8	7.1
16	Chicken broth	+1.1	7.2
17	Glycerine broth	+1.0	7.45
18	Liebig's broth	+0.8	7.0
19	Plain broth	+1.0	6.6
20	Liebig's broth	+0.8	7.0

concentration as measured colorimetrically. Table I illustrates the results of such a comparative study of twenty different batches of media. Similar observations were made by Clark who compared the titration curves obtained in the usual way with the determinations made by the use of the hydrogen electrode.

¹ The significance of the expression $pH=p$ to designate the hydrogen ion concentration will be explained in a subsequent paragraph.

Unfortunately the use of the hydrogen electrode which gives the most accurate knowledge of the reaction of a medium in terms of the concentration of hydrogen ions is not suitable for practical use. Besides being time-consuming² the gas chain electrometric method necessitates special training in physico-chemical technique.

Heretofore the colorimetric method has not given promise, because of the lack of a suitable indicator, and because of the presence of coloring matter in the fluids to be tested. We believe, however, that both of these difficulties have been overcome in the procedure to be described.

PRINCIPLES OF THE COLORIMETRIC METHOD.

Already brief mention has been made of the principle which underlies the use of indicators in the titrimetric method. It was pointed out that the change in color of an indicator during an ordinary titration means that the hydrogen ion concentration of the solution has attained a certain degree characteristic for that indicator. Different indicators show color changes at varying degrees of hydrogen ion concentration. For example, the color of phenolphthalein changes from colorless to red between the values $pH=8.00$ and $pH=10.00$ (1×10^{-8} and 1×10^{-10}); whereas methyl orange passes from its full acid color over into its alkaline color as the hydrogen ion concentration falls from $pH=3.0$ to $pH=4.1$ (1×10^{-3} and 4×10^{-5}). At intermediate points various shades of color are obtained, a certain color indicating a definite hydrogen ion concentration.

Through the investigations of Friedenthal (3) and Salm (4) and of Sørensen (5), we now know the range of color change of a large number of indicators. From the large group studied several have been chosen for practical use, which, because of the extent of their range of color and because of the only slight interference of proteins in the test solutions, are of particular value for studies on hydrogen ion concentration.

In carrying out the colorimetric method it is necessary to have a series of standard solutions of known hydrogen ion concentration, and an indicator exhibiting a wide range of easily distinguishable color changes at hydrogen ion concentrations approximating those of the solutions to be tested. The procedure of making the readings is then quite simple, since it is necessary only to add an equal amount of indicator both to the standard solutions, and to the test solution, and to determine which of the colors in the standard series most closely matches that of the solution tested.

STANDARD SOLUTIONS AND METHOD OF NOTATION.

The standard solutions used in the method to be described were those recommended by Levy, Rowntree and Marriott (6) for the determination of the hydrogen ion concentration of the blood. These consist of standard phosphate mixtures pre-

² McClendon (Am. Jour. Physiol., 1915, XXXVIII, 180, 186) has described a new hydrogen electrode and a direct reading potentiometer, the use of which reduced the time necessary for a determination from forty to about two or three minutes.

pared according to the directions given by Sørensen (7). Since phenolsulphonophthalein shows definite variations in quality of color with small differences in hydrogen ion concentration between $pH=6.4$ and $pH=8.4$, it was chosen by these workers as the most suitable indicator. Experience in the use of these standard solutions containing phenolsulphonophthalein has further emphasized its value as an indicator for this work, not only because of the great breadth of its color range on either side of the neutral point, but also because of the ease with which the various gradations of color can be differentiated, even in the presence of the pigments which occur in most biological fluids. Furthermore, as Sørensen (8) points out, the fact that the phthalein group of indicators is more suitable for use in the presence of proteins or their split-products makes them especially valuable in studying the reaction of biological fluids by the colorimetric method.

In recording hydrogen ion concentration it is most convenient to use logarithmic notation as employed by Sørensen (9) rather than to record the actual concentrations because the significant variation is in the logarithm of the numbers which represent the quantity of hydrogen ions. For instance, $N/10$ hydrochloric acid is $0.091 N$ with respect to its hydrogen ions, and the hydrogen ion concentration is expressed conveniently as 9.1×10^{-2} or simply $10^{-1.04}$, the index, -1.04 , being the logarithm of 0.091 . The method of notation is still more simplified by dropping the 10 and minus sign and designating the hydrogen ion concentration by the expression $pH=1.04$, where pH is the hydrogen ion exponent.

TABLE II.

EQUIVALENTS OF THE LOGARITHMIC VALUES $pH=6.4$ TO $pH=8.4$
IN ACTUAL CONCENTRATIONS OF IONIZED HYDROGEN.

Logarithm pH .	Actual Hydrogen Ion Concentration H .	Logarithm pH .	Actual Hydrogen Ion Concentration H .
6.4	4.0×10^{-7}	7.5 ⁽¹⁾	0.32×10^{-7}
6.6	2.5×10^{-7}	7.6	0.25×10^{-7}
6.8	1.6×10^{-7}	7.7	0.2×10^{-7}
7.0	1.0×10^{-7}	7.8	0.16×10^{-7}
7.1	0.8×10^{-7}	8.0	0.1×10^{-7}
7.2	0.63×10^{-7}	8.2	0.063×10^{-7}
7.3	0.5×10^{-7}	8.4	0.04×10^{-7}
7.4	0.4×10^{-7}		

¹ The hydrogen ion concentration of the blood averages about 0.3×10^{-7} or $pH=7.5$.

In Table II is given the equivalent of the logarithmic notation in actual concentrations of hydrogen ions. Only such equivalents are given which fall within the range of color change for phenolsulphonophthalein.

METHOD.

1. *Method Used in Comparing Colored Fluids.*—One of the greatest obstacles met with in the application of colorimetry to the determination of the ionization of biological fluids is the turbidity and the pigment present in the majority of such fluids. It is obvious that the addition of an indicator to a solution which is already colored gives rise to a tint which can-

not be matched against a standard color scale made up with distilled water. This difficulty has been overcome by various workers in different ways: Sørensen (10), for instance, recommends the addition to the standard solutions of several drops of a solution of some neutral dyestuff so as to compensate for the color of the fluid under investigation. Similarly, turbid solutions can be compared by adding to the standard solutions varying amounts of a freshly prepared suspension of barium sulphate. Such procedures, as must be quite apparent, render the method more complicated and less accurate.

Realizing that this difficulty had to be overcome before the method could be made applicable, we tried various means of freeing such solutions of their color—dialysis, adsorption, and ultra-filtration. The method of dialysis, recommended by Levy, Rowntree and Marriott (11) for determining changes in the hydrogen ion concentration of the blood was first tried. This procedure, although invaluable for blood determinations, cannot be made applicable to studies on the hydrogen ion concentration of biological fluids. As we know, these fluids contain substances, chiefly the phosphates, carbonates, and colloids, which tend to preserve the original hydrogen ion concentration of the solutions. The value of these so-called "buffers" must be determined, if such fluids are to be adjusted to any desired ionization. In tests upon the dialysate, however, the influence of these "regulators" is not fully ascertained. The use of filtration through collodion membranes, although more accurate, is more difficult and equally objectionable for the reasons just given.

The removal of coloring matter by adsorbents like charcoal and Kieselguhr was early discarded, because both of these substances contain free alkali which changes the hydrogen ion concentration.

In order to obviate all of these difficulties, we have constructed a simple device* (Fig. 1), whereby the medium tested serves as a background for the standard test color to which it imparts its own characteristic quality of color, thus making the color of the fluid to be tested directly comparable with the standard test solutions. This apparatus* consists of the parts pictured (Fig. 1): A block of wood about three inches long, two inches wide and one and a half inches thick serves for the construction of the comparator. Into this block four holes, *A, B, C, D*, are bored *vertically*; these are arranged in two pairs, one beside the other. Slots *S* and *S'* are then cut through the holes. If test tubes of the proper thickness are now inserted into holes *A, B, C*, and *D*, and the apparatus is held against a white background, the light in passing through each slot must pass through the two pairs of tubes.

* After constructing our instrument we found that Walpole (Jour. of Biol. Chem., 1910-1911, V. 207) has made use of the same principle for reading colored fluids. Instead of having the four test tubes arranged parallel to one another, he has placed them end on in pairs.

² Inasmuch as the test consists merely in comparing the qualities of colors and not their intensities, as is done in ordinary colorimetry, it was thought advisable to use the term comparator rather than colorimeter for the apparatus.

The tube in *A* is the standard comparison tube of known hydrogen ion concentration. Into the hole *B* is placed the tube containing the fluid to be tested plus the correct amount of indicator. To compensate for the color of the test fluid a sample of this without indicator is placed into *C* which is just behind the standard test color. Into *D* is placed a tube containing distilled water; this tube is used merely to make the field of view of both slots of the system similar.

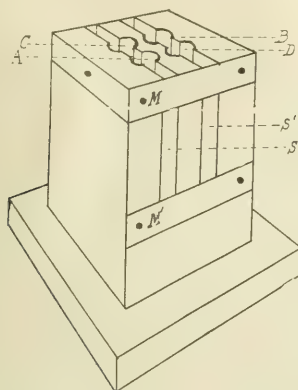


FIG. 1.—Diagram of Comparator. Into the holes *A, B, C, D*, are placed the four test tubes: *A* receives the standard comparison tube; *B* receives a tube containing the medium plus indicator; into *C* is placed the test solution to compensate for the natural color of the medium, and into *D* a test tube containing water. *S* and *S'* are the slots through which the colors are matched. *M* and *M'* are metal bands designed to equalize the portions of color fields exposed to view.

The titrations are most conveniently carried out in a specially constructed tube shown in Fig. 2. The acid or alkali used for

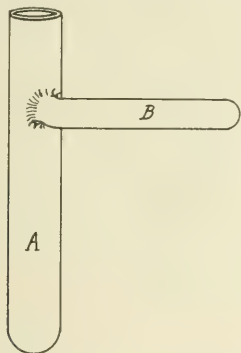


FIG. 2.—Diagram of Titration Tube. Test solution and acid or alkali are mixed in part *A*; comparisons of the color of the solution are made in part *B*, which is inserted into hole *B* of the comparator. Tube *B* is offset from part *A*, in order that part *A* will not crowd the other tubes in the comparator.

the titrations is run into the larger tube and thoroughly mixed with the test fluid. For making the comparisons, the fluid is run into the side tube, which is of the same internal diameter

and thickness as tubes *A, C*, and *D*; this tube is inserted into the hole *B* of the comparator.

In making a reading that standard tube is chosen which at first glance appears most nearly like the color of the fluid tested. Then comparisons are made with the standard just above or below in the scale, until the closest approximation is obtained. In this way it is possible to read quite accurately between any two parts on the standard scale. It has been our experience that this method of making readings is applicable to most of the biological fluids possessing any great transparency and whose natural color is not too intense. For determinations upon yellow and straw-colored fluids it is especially useful, since phenolsulphonephthalein, in the presence of an alkali, imparts to them a brownish red tint, which can be readily matched by blending the natural color of the medium with that of the appropriate standard solution, as is done in the comparator.

2. *Preparation of the Reagents.*—In addition to the indicator *N/20* acid and alkali are needed for standardization and *N/1* acid and alkali for adjusting the medium to the desired concentration of ionized hydrogen.

The same strength of indicator is used in the titrations as was added originally to the standard test solutions. This is an aqueous 0.01 per cent solution of phenolsulphonephthalein made up as follows: A measured volume of indicator is obtained from a standardized solution* (1 cc=6 milligrams) is added to the required amount of distilled water. Of this a measured volume is taken and boiled for several minutes to expel the carbon dioxide. The solution is then made up to the original volume, so as not to alter the concentration of the indicator.

In order to keep the concentration of indicator during titration the same as its concentration in the standard comparison tubes (0.3 cc. to 3 cc. or 1 to 11), the solutions of *N/20* acid and alkali used for titration are so made up that one-eleventh of their volume consists of the indicator solution. For instance, two liters of such a solution[†] are prepared according to the following formula:

Acid or alkali <i>N/10</i>	1000 cc.
Indicator, 0.01 per cent.....	182 cc.
Distilled water to make.....	2000 cc.

These solutions containing the indicator are used, however, only if the method is carried out according to procedure B, described below.

The normal solutions of acid or alkali are measured, sterilized and again made up to the original volume. Adjustments

*This is the well-known standardized solution of phenolsulphonephthalein prepared by Hynson, Westcott & Company, of Baltimore, Md., for testing kidney function.

†This solution must be protected from light, moisture, and carbon dioxide. If the vessel containing it is covered with a box and the glass tubing leading from it to the graduated pipette is surrounded with an opaque paper, the solution can be kept for a long time without fading of the indicator. The solution is protected from moisture and carbon dioxide by inserting into one opening of the stopper a tube containing potassium hydroxide and calcium chloride.

in the reaction of bacteriological culture media are to be made after sterilization with sterile acid or alkali for reasons which will be discussed later. For the adjustment of other culture fluids, however, no such precautions are necessary.

3. *Preliminary Test.*—The medium is tested first to ascertain what its ionization is before adjustment. This preliminary test can be carried out quickly: To 3 cc. of fluid is added 0.3 cc. of a 0.01 per cent solution of the indicator, the fluid being read directly in the comparator. In most instances the culture fluid has been roughly adjusted by the usual methods so that its reaction falls within the limits of the scale ($pH=6.4$ to $pH=8.4$). If the medium has not received a preliminary adjustment of reaction, it may be too acid or too alkaline to be read directly. In that event titrations are carried out in the manner to be described. From such titrations is determined the amount of acid or alkali needed to bring a liter of the medium tested from its present reaction to a desired optimal ionization.

4. *Method of Titration—Procedure A.*—It may be well, before describing the manner of carrying out the titration which was finally adopted because of its greater simplicity, to present the method as it was first tried. In procedure A the several steps in the titration, instead of being combined as in procedure B to be described below, are carried out separately.

To each of ten test tubes* of the same internal diameter and thickness as those containing the standard solutions are added 5 cc. of the medium tested. From a one cubic centimeter pipette graduated into hundredths is added N/20 acid or alkali, 0.1 cc. to the first tube, 0.2 cc. to the second and so on up to 1 cc. to the tenth tube. An amount of the indicator solution corresponding to one tenth of the whole volume is now added to each tube. The amounts of the acid or alkali and of the indicator solution added to each tube in this procedure are given in Table III. This gives a series of tubes containing

TABLE III.

AMOUNTS OF N/20 ACID OR ALKALI AND AMOUNTS OF INDICATOR SOLUTION REQUIRED FOR EACH OF 20 TUBES TITRATED ACCORDING TO PROCEDURE A.

No. of Tube.	1	2	3	4	5	6	7	8	9	10
N/20 acid or alkali in cc.	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Amount of indicator in cc.	0.31	0.32	0.33	0.34	0.35	0.36	0.37	0.38	0.39	0.40

No. of Tube.	11	12	13	14	15	16	17	18	19	20
N/20 acid or alkali in cc.	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
Amount of indicator in cc.	0.41	0.42	0.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50

*The titration of ten such tubes will ordinarily suffice if the medium has been roughly adjusted to begin with. In Table III are given the amounts of alkali and indicator to be added to 20 tubes should it be necessary to carry the titrations above the tenth tube.

the medium in a graded scale of hydrogen ion concentration and comparable in quality and intensity of color with the standard comparison tubes.

From among the ten tubes is chosen the one whose color most closely approximates that of the standard solution to which it is compared. The desired ionization may lie at a certain point between any two of the tubes of the series, in which case it is necessary to interpolate. If, for instance, tube No. 1 corresponds to the value $pH=7.3$ and tube No. 2 to $pH=7.6$, and the hydrogen ion concentration desired in $pH=7.5$, the correct amount of N/1 acid or alkali to be added will lie on the curve two-thirds of the distance between that required to obtain the ionization 7.3 and that needed to give the value $pH=7.6$.

5. *Procedure B.*—For practical use it has been found advisable to combine some of the steps in the titration so as to increase the rapidity of the method without affecting its accuracy. Instead of adding the alkali and the indicator separately to each tube, the two solutions have been combined in the manner already stated in the paragraphs on the preparation of the reagents. This solution is kept in a vessel shielded from the light and the apparatus is so arranged that the solution can be delivered directly into a graduated one-cubic-centimeter pipette, provided with a ground glass stopcock on the principle of a burette. With such an arrangement, the titration can be carried out quickly and the amounts of acid or alkali used are read directly on the pipette.

The method is further simplified because the titrations can be carried out with 3 cc. instead of 30 cc. of the medium, as in procedure A. Furthermore, greater accuracy is attained, since the readings in hundredths of a cubic centimeter can now be made directly on the pipette. This does away with the necessity of interpolation for amounts between tenths of a cubic centimeter—a process which is subject to inaccuracies. Readings on the pipette in terms of the N/20 solutions used for titration can be converted directly into N/1 acid or alkali per liter by reference to Chart I, which will be described below.

The method of making the comparisons is identical for both procedures, A and B.

6. *Method of Adjusting the Media.*—The manner of adjusting the medium to the desired hydrogen ion concentration may be made clear by a specific example. The medium which has been roughly standardized to +0.5 or +1.0 (Fuller scale) is sterilized in amounts, the volumes of which have been previously measured. This may be done in ordinary flasks, which have been graduated before use to a definite volume, so that any fluid lost by evaporation during sterilization may be made up by the addition of sterile distilled water. If it is desired, for example, to adjust such a medium to the hydrogen ion concentration of the blood, which corresponds to about $pH=7.5$ on the scale, a 3 cc. sample is titrated, as already explained, until a color is obtained which matches 7.5 on the scale. Now the amount of N/20 alkali used is read directly on the graduated pipette. Should this reading be 0.46 cc., for instance, its equivalent in terms of N/1 alkali per liter would

be 9 cc. This conversion of N/20 into N/1 alkali can be made directly from Chart I, on which the N/20 solution is plotted as abscissæ and the N/1 solution as ordinates. If now 9 cc. of N/1 alkali be added to a liter of the medium, the desired hydrogen ion concentration will be obtained. Should the medium be alkaline to start with, it is, of course, necessary to titrate with N/20 acid and to adjust the medium with an equivalent amount of normal acid. For this correction the lower curve of Chart I is used.

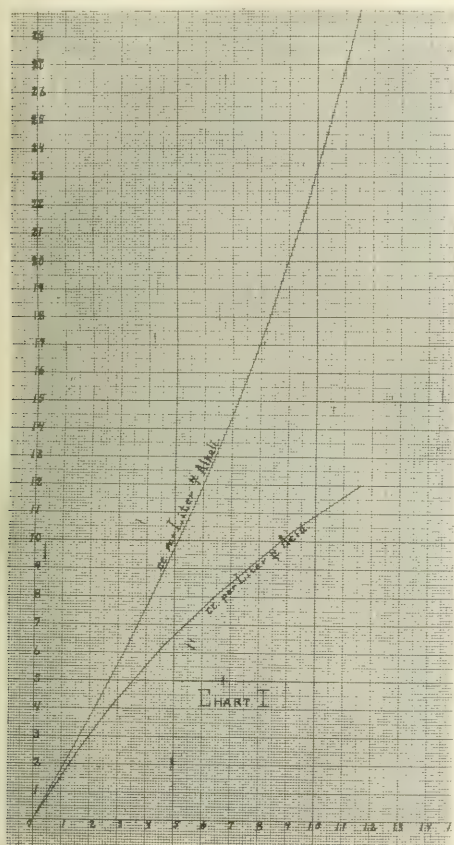


CHART I.—Curves indicating the actual amounts of N/1 acid or alkali necessary to adjust one liter of medium to the desired hydrogen ion concentration, as indicated by the amount of N/20 acid or alkali used.

Although the titrations are made with N/20 acid or alkali solutions in order to insure greater accuracy in measurement, it is desirable for practical purposes to make the adjustment with normal acid or alkali so as not to dilute the media too much. The conversion of the amounts of N/20 solution used into the corresponding amounts of N/1 solution required per liter is accomplished most readily and accurately by plotting

a curve. Such a curve must take into account three factors: the alteration in volume due to the addition of concentrated rather than dilute alkali or acid; the differences in the dilution of the "buffers" of the medium, in the one instance by N/20 solution, and in the other by N/1 solution; and lastly, the degree of correspondence between the N/20 solution used for the titration and the N/1 solution used for adjusting the medium.

Only the first of these conditions can be satisfied by a curve plotted from theoretical calculations. In fact the use of such a curve has convinced us of its inaccuracy. In order to correct for all three of the variables, it was found necessary to plot a curve from data obtained by the titration of an average laboratory medium. This is done in the following manner: To five 25 cc. samples from each of two media, one originally acid and the other alkaline in reaction, was added N/1 alkali and acid in the amounts of 0.1 cc. to the first sample, 0.2 cc. to the second and so on up to the last. From each of these samples 3 cc. were then withdrawn and to each was added 0.3 cc. of the indicator. A 3 cc. sample of the same medium was now titrated with N/20 alkali or acid, after the addition of 0.3 cc. of the indicator solution, until its color matched successively the color of each of the five tubes. The amounts of N/20 solution required were plotted as abscissæ and the corresponding amounts of N/1 solution as ordinates.

The upper and lower curves of Chart I express the relation existing between the number of cubic centimeters of N/1 alkali or acid per liter of medium and the number of cubic centimeters of N/20 alkali or acid per 3 cc. of medium necessary to bring about the same hydrogen ion concentration. In this way account is taken also of the effect upon ionization of the "buffers," by the dilution of the medium in the one instance by N/20 solution and in the other by N/1 solution. Such curves plotted for an average medium* will be found true for almost all similar media.

It is recommended that each worker using this procedure plot such reference curves. This will add greatly to the accuracy of the method, since, besides correcting for volume and dilution of "buffers," these curves correct also for any error which may arise from lack of correspondence between the N/20 solutions used for titration and the N/1 solutions used for adjusting the media.

In order that the application of this method may yield satisfactory results in the adjustment of bacteriological culture media, it is essential, in the first place, that the medium be roughly adjusted in the beginning, and secondly, that the correction in reaction be made with a sterile acid or alkali. Such a rough correction conducted in the usual manner serves a two-fold purpose: (1) it brings the reaction within the range of the standard scale, thus making a direct reading in terms of hydrogen ion concentration possible; and (2) it necessitates the addition of smaller quantities of acid or alkali for the

*Most of the media tested in this laboratory were prepared by extracting meat for 18-24 hours in the cold and then adding to this extract one per cent peptone, either Witte or Chapoteaut.

final adjustment of the sterile medium. This obviates the dilution of the active ingredients and the possibility of precipitate formation, which may result from the addition of too large quantities of acid or alkali.¹⁰

The fallacy of correcting by the titrimetric method the reaction of a medium before sterilization applies all the more to the procedure under consideration. It is now well known that media show not only an increase in titratable acidity after sterilization (12), but, as would be anticipated, sterilization changes the equilibrium of hydrogen and hydroxyl ions (13). This change may or may not be accompanied by precipitation. It follows, that adjustments in the hydrogen ion concentration made before sterilization do not hold for media after they have been sterilized. This is all the more true of the finer adjustments in the ionization which are obtainable by the procedure outlined. It has, therefore, become the custom of some workers (14) to correct their media by adding a sterile acid or alkali to the sterilized medium.

The matter is much simplified, however, where the question of sterilization does not enter, as in the case of other culture fluids, for instance, those containing active enzymes. The latter can be readily adjusted to any optimal ionization directly, if their range of activity lies within the concentration of hydrogen ions represented by the standard solutions used.

RESULTS OF THE METHOD.

In order to determine the accuracy and the usefulness of the method, titrations were carried out on various samples of media—bouillon, agar, and gelatin, chosen at random from the different batches in the laboratory. Most of these had been adjusted previously according to the Fuller scale, so that their reaction fell within the limits of the colorimetric scale. In practice such media are usually found acid, necessitating, therefore, an addition of alkali to adjust them to the desired reaction. In order to test out the applicability of the method to the adjustment of media found to be too alkaline, titrations were also carried out with N/20 acid instead of alkali upon samples which had been previously made alkaline.

After determining the amount of N/1 alkali or acid needed to bring the test medium to the desired hydrogen ion concentration, this amount was added to a 25 cc. sample and a determination again made of the adjusted medium.

Forty-nine determinations were made upon twenty-three different samples of media. The results of the titrations are recorded in Tables IV and V. In Table IV are listed the various media just as they were prepared for use in the laboratory, while in Table V are recorded the results of titrations of media made alkaline for experimental purposes.

It will be seen that, for the most part, the correspondence between the hydrogen ion concentration desired and that obtained by the addition of the correct amount of alkali or acid

is very close. Such accuracy in titration is readily obtained after sufficient familiarity with the technique and the standard color scale.

In several instances determinations of the hydrogen ion concentration of solid media were made. Media containing agar or gelatin were first rendered fluid by bringing them to the proper temperature. To the fluid solution was then added the indicator. The medium was inverted in the test tube several times to distribute the color evenly, and allowed to solidify. Determinations of the hydrogen ion concentration of the solidified medium could then be made directly in the comparator. Most of the samples tested in this manner were sufficiently transparent to make a color comparison extremely accurate. In a few cases samples of agar were adjusted with the calculated amount of acid or alkali and determinations of the adjusted samples of the solidified media were made, as in the case of fluid media. These tests convinced us of the usefulness of the method for the determination of the hydrogen ion concentration of solid media.

USEFULNESS AND APPLICABILITY OF THE METHOD.

In discussing the practice of adjusting media by the method of titration in general use, attention was called to the variations in hydrogen ion concentration possessed by media adjusted to the same point on the Fuller scale. In spite of these variations in reaction, however, most bacteria have been successfully cultivated. Clark's experience has been that *B. coli* and certain streptococci will grow in media with hydrogen ion concentration values varying from $pH=5.5$ to $pH=9.0$. This fact is now readily explained by the presence in such media of "regulators" or "buffers." These, as already explained, prevent rapid changes in hydrogen ion concentration, which may be produced by the metabolic products of bacterial growth. This explains the value of an infusion rich in "buffers" (principally the phosphates, carbonates, and amphoteric proteins) whose ionization is little altered by a considerable variation in titratable acidity.

Chart II illustrates graphically the difference in the "buffer effect" of several such media, as measured by the amount of N/20 acid or alkali needed to bring each from one concentration to another given concentration of hydrogen ions. It will be observed that the media rich in "buffers" show flatter curves than those that are poor in "buffers," for the reason that a transition from one point on the scale to another requires more acid or alkali. Similar curves obtained by the use of the hydrogen electrode have been plotted by Clark (15). It is more simple, however, to obtain such curves by using the colorimetric method. Their value rests in the important information they give concerning the "buffer" content of a medium upon which depends, in large measure, its usefulness for the growth of bacteria.

¹⁰ Readings should be made on the solidified medium at a constant room temperature, since the hydrogen ion concentration changes with the temperature.

¹⁰ As Clark (p. 127) points out, proteins exist in solution only within certain narrow limits of hydrogen ion concentration, and the precipitation of these and other substances of a complex medium occurs as the hydrogen ion concentration is changed.

TABLE IV.

TITRATION OF ACID MEDIA SHOWING VALUE OF pH DESIRED AND THAT OBTAINED BY ADDING CORRECT VOLUME OF N 1 ALKALI TO A 25 CC. SAMPLE OF MEDIUM.

No. of Exp.	Date.	Media.	Titration by Fuller Scale.*	Preliminary test.	Standard desired.	N 20 alkali in cc.	N 1 alkali added per 25 cc.	Value of pH obtained.	Remarks.
1	Aug. 6	Veal-infusion.	+1.0	Below 6.4	7.5	0.46	0.225	7.45	
2	Aug. 7	Plain broth.	+0.8	6.9	7.6	0.17	0.073	7.55	
3	Aug. 12	Liebig's broth.	+0.8	6.9	7.6 7.7	0.195 0.20	0.087 0.095	7.55 7.7	Medium poor in "buffers" as shown by titration curve.
4	Aug. 16	Plain broth.	+0.8	7.15	7.6 7.9 8.2	0.13 0.195 0.285	0.06 0.088 0.13	7.6 7.9 8.15	
5	—	Extract.	+1.0	6.9	7.5 7.9	0.08 0.21	0.04 0.096	7.55 7.9	Plotted as Curve V, Chart II; medium poor in "buffers."
6	Aug. 11	Ox-heart broth.	+1.1	6.9	7.4 7.6 7.8	0.25 0.30 0.35	0.114 0.14 0.164	7.4 7.55 7.75	Plotted as Curve VII, Chart II.
7	Aug. 11	Ox-heart broth—no peptone.	—	Below 6.4	7.2 7.3	0.36 0.43	0.17 0.21	7.15 7.3	Plotted as Curve VI, Chart II.
8	Aug. 16	Chicken broth.	+1.1	7.25	7.6	0.48	0.23	7.65	
9	Aug. 17	Plain agar.	+1.0	7.1	7.9	0.26	0.12	7.9	
10	Aug. 17	Sugar-free broth.	—	7.2	7.4 7.6	0.185 0.26	0.085 0.12	7.45 7.55	
11	Aug. 17	Plain broth.	+1.0	6.9	7.3 7.7 7.9	0.195 0.275 0.375	0.09 0.13 0.18	7.3 7.65 7.9	
12	Aug. 17	Glycerine broth.	—	7.45	7.7 7.9	0.08 0.15	0.04 0.07	7.7 7.9	
13	Aug. 26	Liebig's broth.	+0.9	Below 6.4 Below 6.4	7.0 7.4 7.7 7.5	0.285 0.35 0.435 0.37	0.13 0.17 0.21 0.19	7.05 7.35 7.7 7.5	
14	Aug. 30	Ox-heart broth.	—	6.9	7.3	0.17	0.08	7.25	
15	Aug. 30	Ox-heart broth plus 10% bile.	+1.0	6.9	7.6 7.4	0.30 0.25	0.15 0.12	7.55 7.35	
			—	7.1	7.7	0.21	0.1	7.65	

* Recorded readings by Fuller method were made before sterilization.

TABLE V.

TITRATION OF ALKALINE MEDIA SHOWING VALUE OF pH DESIRED AND THAT OBTAINED BY ADDING THE CORRECT VOLUME OF N 1 ACID TO A 25 CC. SAMPLE OF MEDIUM.

No. of Exp.	Date.	Medium.	Titration by Fuller Scale.	Preliminary Test.	Standard desired.	N 20 acid in cc.	N 1 acid added per 25 cc.	Value of pH obtained.	Remarks.
1	Aug. 18	Plain broth.	—	8.3	7.9 7.4	0.33 0.49	0.12 0.16	7.9 7.45	Plotted as Curve I, on Chart II.
2	Aug. 19	Sugar-free broth.	—	8.3	7.8 7.4 7.3	0.21 0.33 0.44	0.08 0.115 0.15	7.85 7.45 7.3	Plotted as Curve II, on Chart II.
3	Aug. 20	Liebig's broth.	—	7.7	7.2	0.10	0.04	7.2	Plotted as Curve III, Chart II.
4	Aug. 20	Liebig's broth—no peptone.	—	8.4	7.9 7.6 7.3	0.44 0.64 0.82	0.15 0.20 0.24	7.9 7.6 7.3	
5	Aug. 21	Ox-heart broth—no peptone.	—	—	7.5 7.1	0.33 0.52	0.12 0.17	7.5 7.1	Plotted as Curve V, Chart II.
6	Aug. 24	Ox-heart glucose broth.	—	7.6	7.1	0.10	0.04	7.1	
7	Aug. 26	Liebig's broth.	—	8.35	7.9 7.5 7.2	0.21 0.44 0.56	0.08 0.15 0.18	7.9 7.55 7.25	
8	Aug. 30	Ox-heart broth plus 10% bile.	—	8.3	7.9 7.3	0.33 0.56	0.12 0.18	7.85 7.3	

The real usefulness of the colorimetric method, however, must be sought in its greater accuracy and in its wide scope of applicability. It will be found of great value in the adjustment of the hydrogen ion concentration of media for organisms

upon the morphology, mutations and metabolisms of organisms, bacteria²² and also protozoa. Whether the colorimetric method in its present form is suitable as a substitute for those now in general use in bacteriological laboratories can be decided only after it has been accorded a more extensive application.

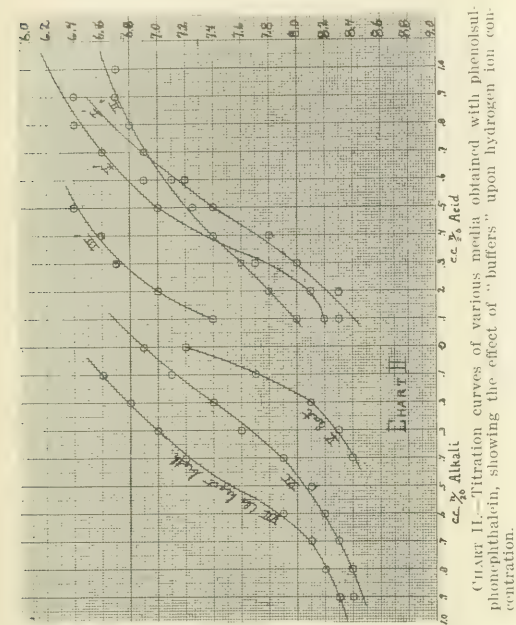
Already we have found the method, with some modifications, useful in determining the reaction of other biological fluids. Further studies in this direction are now being carried out in this laboratory.

In conclusion, we wish to express our indebtedness to Drs. Rowntree and Marriott for providing us with a set of the standard test solutions, made under their supervision by Mr. Dunning, of Hynson, Westcott & Company, Baltimore, Md., and for valuable suggestions regarding their use.

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²² Blumenthal (*Ztschr. f. klin., Med.*, 1895, XXVIII, 223) has shown that the reaction of the medium influences appreciably the relative proportions of the end-products of fermentation and putrefaction.



which are more sensitive to the reaction of their culture fluids. The method is comparable in a way to the fine adjustment of a microscope, the method of titratable acidity serving only to adjust media coarsely for the growth of the average organism. Its further usefulness will be found in careful studies

HODGKIN'S DISEASE OF THE INTESTINES. WITH REPORT OF A CASE.

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It has not been a great while since the conception of Hodgkin's disease as an affection beginning always in the glands of the neck, or at least in a superficial gland group, has been questioned.

Yates¹ defines Hodgkin's disease as "an infectious non-contagious affection due to *B. hodgkinii*. It is characterized by a somewhat variable, though definite, reaction in the lymphatic and perilymphatic structures, specific changes in the blood picture, and by the manifestation of little or no tendency to spontaneous recovery." That there is a primary mediastinal type of this disease is now recognized. The tumor

formations confined to the intestines, however, are very uncommon, and a case which has come under our notice seems worthy of record in the literature of this disease.

Bunting,² in 1910, reported his observations upon the increase of blood platelets and megalokaryocytes in Hodgkin's disease. Not only were the platelets markedly increased in number, but large forms were numerous, and many of these masses revealed pseudopod-like processes.

In 1911,³ he reported upon a characteristic blood picture in the disease. This consists principally in an increase of the large endothelial-like cells, so-called transitional, together

with the previously noted increase in number and size of the platelets. In the four years since this publication, there has been abundant opportunity to confirm his original observations and to extend them so that one is able, from the blood picture, to tell whether a patient is improving or retrogressing.

Steiger,⁴ in a long and rather elaborate discussion of Hodgkin's disease, comes to the conclusion that the blood picture is characterized by a leucocytosis of the polymorphonuclear type. He makes no mention of platelets. It is possible (although it is not so stated) that he used Ehrlich's stain. Under such circumstances, he would have failed to see the platelets. His blood picture tallies with that found by Bunting in the final stages of the disease, when the platelets actually are diminished.

Bunting and Yates,⁵ in 1913, reported the discovery of a diphtheroid bacillus, showing marked pleomorphic characters, in three cases of Hodgkin's disease. Later they reported that they had reproduced the disease in a monkey. The characteristic blood picture was present.

In a later communication,⁶ they report experiments which seem to leave no doubt of the transmission of the disease from one monkey to another. These cultural results have been confirmed by Rosenow,⁷ Steele,⁸ Verploegh,⁹ Kehrer, Von Hoogenhugze, and others. The evidence now at hand seems to justify the definition of Yates given above. Clinically, we have had an opportunity of observing cases beginning in the mediastinum, as well as in other groups of glands besides the cervical.

The case here reported is the only one of its kind which has come under our notice, and one of the very few in the literature.

D. S., a Bulgarian, single, aged 27, common laborer by occupation, was admitted to the Milwaukee County Hospital, April 9, 1914, complaining that he was "sick in his stomach." He had never been ill, smoked moderately, and denied venereal disease. For about eight months he had had intermittent pain in the stomach after eating, which was not severe enough, at first, to force him to stop work. The pain, however, had gradually increased, he had vomited occasionally after meals, had become weak, and lost strength and weight so that he had been obliged to stop work in January. Since the onset of his trouble, he had had almost constant diarrhea. There had also been an intermittent cough.

He was only fairly well nourished. There were a few mucous rales at the lung apices, and slight impairment of the percussion note at both bases.

The abdomen showed a "curious distension below the umbilicus, as with gas, with apparent constriction just below the costal margin." There was no increase in liver dullness. There were no masses palpable. He was in the hospital only a few days. The most probable diagnosis seemed to be pulmonary tuberculosis, with a dry peritoneal tuberculosis.

He was readmitted May 2, 1914, having grown much weaker and more emaciated. The pain in the stomach was worse, the vomiting after meals more frequent. He was not coughing or expectorating. There was flatness over both bases of the lungs. The liver did not reach the costal margin. The appearance of the abdomen was similar to that observed on the previous admission. There were no enlarged glands anywhere.

Some fluid was removed from the right pleural cavity. The leucocytes were 7000. Differential count (Hastings' stain) showed polymorphonuclears, 60%; mat. and immat. lymph., 34%; trans.

(end.) 6%; bas., 1%. The records made no mention of platelets. There was no occult blood in the stools. Several examinations for tubercle bacilli in the sputum were negative. The urine was normal. On the 13th, the leucocytes were 16,200. The patient gradually grew weaker, and died rather suddenly, with obscure abdominal symptoms, subnormal temperature and only slightly increased pulse rate, on May 23d.

Autopsy (Dr. Kristjanson), 26 hours after death.

Anatomical Diagnosis.—Acute general peritonitis, with perforation of jejunum; diffuse and nodular thickening of intestines; enlargement of mesenteric glands; acute splenic tumor; slight pleural effusion (right side); edema of lungs.

General Appearance.—The body is that of a rather poorly nourished and emaciated young white male, 150 cm. in length. There is marked post-mortem discoloration of the skin over the back of the neck and upper portion of the chest, down to the third rib. There is a slight greenish tinge to the skin over the lower half of the abdomen. The pupils are unequal; the left measures 4 mm., the right, 5 mm. in diameter. Rigor mortis is very slight in the extremities.

Abdomen.—There is some distension of the abdomen, with a tympanic note over the central portion, but dullness in both flanks. The abdominal cavity contains about three liters of a foul-smelling, brownish semi-fluid material. The small intestines are distended and discolored and in several places are glued together by an acute fibrinous exudate. There are many nodular enlargements in the wall of the intestines. The mesenteric glands are much enlarged. The diaphragm stands at the fifth rib on the right side, at the fourth interspace on the left. The liver projects about 4 cm. below the costal border. The stomach is somewhat distended, and the anterior wall and adjacent parietal peritoneum are covered with fibrin. There are a few chronic adhesions about the spleen.

Thoracic Cavity.—The lungs nearly fill the respective pleural cavities and they meet in the median line. On the right side are a few chronic fibrous adhesions about the junction of the lobes, uniting them to the chest wall. The left lung is free; there are no adhesions about the apices. There is a small amount of bloody fluid in the right pleural cavity. A few small palpable glands are found in the anterior mediastinal space. The myocardium is brownish-red in color and fairly firm.

Lungs.—The right lung is rather voluminous; it weighs 470 grams. There are a few adhesions between the lobes. In the upper portion of the lower lobe is a small nodule, hard and firm, measuring 5 cm. in diameter, composed of encapsulated calcareous material. The dependent part of this lung is a little firmer than normal, and on section there is an excess of blood and serum. The left lung is a trifle smaller than the right. It weighs 420 grams, and is similar in appearance to the right lung. The dependent portion contains bloody fluid.

Spleen.—The spleen is quite large; it weighs 280 grams. It is bound by firm adhesions to the diaphragm. There are also adhesions about the pedicle uniting it to the transverse colon. The external surface is smooth and pale blue in color, except where it is spotted with grayish-white areas of fibrous thickening of the capsule. The cut surface shows the trabeculae radiating from the capsule through the soft, friable, congested pulp, in which the lymph-nodes are no longer visible.

Liver.—The liver is somewhat enlarged (1600 grams). It is firm, and of a deep reddish-brown color. On section blood drips from it freely, and it presents a peculiar mottled appearance. The lobulation is indistinct. The gall-bladder is partially filled with a viscid dark-brown fluid.

Pancreas.—The pancreas shows no change on gross appearance.

Stomach.—The stomach is normal in appearance.

Intestines.—The small and large intestines and mesentery were removed in one piece. The mesentery is a mass of soft lymph-

glands that vary in size from 1 to 4 cm. in diameter. On section they seem to be confined within a definite capsule; the cut surface shows a fairly uniform whitish-gray tissue, from which a small amount of grayish material can be scraped. None of these glands show any evidence of suppurative or caseation.

Approximately 46 cm. from the pyloric end of the stomach, in the course of the jejunum, is a small opening, about 4 mm. in diameter in the serous coat of the bowel, directly opposite to the mesenteric attachment. When the intestine is opened at this point, there is found a small ulcerating area, through the base of which is a small perforation, corresponding to the opening in the external surface of the bowels. This ulcer is 9 mm. in diameter, with fairly smooth edges; the base around the perforation is bathed in a grayish necrotic material.

Throughout the entire extent of the wall of the small intestine are small and large nodular bodies. There is also a uniform thickening of the intestinal coats. About the junction of the jejunum and the ileum are several small loops of intestine, united by chronic fibrous adhesions. In the proximal portion of the mass thus formed are nodular bodies in the wall of the intestine. These, apparently, are small glands, having on section the gross characteristics noted in the mesenteric glands. These nodular masses and the thickening of the wall become more marked as one approaches the lower end of the ileum and cecum.

In the upper third of the ileum, there is a great enlargement of the intestine, which measures 7 cm. in diameter; and when a longitudinal incision of 7 cm., the length of the tumor mass, is made, the intestinal wall is found to be thickened, and measures 2 cm. On examining the interior of the bowel at this point, one finds that the transverse folds are for the most part obliterated, and there are irregular soft masses protruding into the lumen of the gut. Between this point and the cecum are encountered numerous nodular enlargements, with thickening of the intestinal walls; but these are not so pronounced as the ones just described.

About 3 ft. from the cecum, along the mesenteric attachment of the small intestines, is a tumor mass, 5 x 3 x 2.5 cm. It is covered by the serous coat, and the cut section has a grayish-white granular appearance.

The distal end of the ileum, the cecum, and a tumor mass in the mesentery are united by adhesions, forming a large nodular mass. The appendix lies curled up in a fold of this big mass. It, however, does not seem to be involved in the growth. The wall of the cecum is very much thickened, making up the major portion of the tumor. There are a few small palpable glands along the mesenteric attachment of the ascending colon. There seems to be a uniform thickening of the wall of the large bowel, yet no nodular bodies are found in the submucosa. The solitary follicles and Peyer's patches are, in places, enormously thickened, raised, and of a dull gray color.

The right kidney is normal in size and shape. The capsule strips off readily, leaving a smooth, but slightly mottled surface. On section, the cut surface presents a fairly normal appearance. The cortex is 4.5 mm. in thickness, and shows numerous reddish streaks, extending from the capsule towards the papillae. The Malpighian corpuscles are not discernible in the cut section. The left kidney presents no essential difference. Blood drips from the cut surface of both kidneys. The suprarenals are very small, and on gross appearance present no visible pathological changes.

Bladder and Prostate.—The bladder is not thickened and shows no abnormal condition. The prostate is not enlarged.

Glands.—The cervical, axillary, mediastinal and femoral glands are not palpable.

MICROSCOPICAL EXAMINATION.—Sections of the lungs show only edema. Large multinucleated cells are seen in the capillaries. These do not seem to be increased in number.

Liver.—There is general infiltration, with small and large round cells, the former having the usual structure and size of lympho-

cytes, the latter showing some variation in size, always being considerably larger than the former, with fairly deeply staining nucleus and a considerable amount of protoplasm. The inter-columnar liver spaces are separated by the extensive infiltration. Scattered throughout in the portal spaces are collections of lymphoid cells which form minute nodules. The cells in these nodules are of various kinds, and now and again one finds a giant cell of the Reed type, with vesicular nuclei, and of another type with small, deeply staining nuclei.

Spleen.—There is marked congestion of the organ throughout. The pulp contains little that resembles normal spleen. There is a great variety of cells, mostly round, with great numbers of plasma cells. The Malpighian bodies show profound changes. There are hyaline arteries indicating where the vessels have been; or at times there are ill-defined collections of round cells—spaced apart—with an arteriole, the wall of which has undergone hyaline degeneration. The splenic sinuses are large and crowded with blood cells. Many giant cells, containing from 5 to 10 vesicular nuclei, are found scattered through the pulp. There is a great increase in new connective-tissue fibrils, and many fibroblasts.

Intestines.—Sections taken from various portions show varying degrees of the same general picture. The epithelium is not disturbed; the basement membrane is present. The great increase in thickness of the gut is found to be due to the enormous hyperplasia of the submucous coat and dense infiltration of both muscular coats to the serosa. The individual muscle fibers are widely separated by masses of cells streaming in from the submucosa. These are mostly typical lymphoid cells, and the first impression is that the growth is a lymphosarcoma. Close study shows that there is proliferation of the reticulum; there are places where endothelioid cells are fairly numerous, and giant cells are scattered throughout. The eosinophiles are few in number. The picture is that of Hodgkin's disease.

Sections from the intestines were stained by Gram's method and careful search was made for Gram-positive bacilli. Some structures were found which were believed to be bacilli.

Some of the affected tissue was placed in antiformin, according to the method of Fraenkel and Much. We confess an inability to state that the particles taking the stain on the slide were or were not fragments of bacilli. We feel that, in the absence of a differential stain, no one can say positively that fragments on a slide after antiformin treatment of the tissue are granular forms of bacilli.

Cultures were not made, as we felt it would be useless to attempt to grow specific organisms in the face of the intense colon infection of the peritoneal cavity.

Wells and Mayer," in 1904, reporting a case of "pseudo-leukemia gastrointestinalis," were able to find only six cases in the literature showing extensive changes in the lymph tissue chiefly or solely of the gastrointestinal tract. In their case the chief hyperplasia was in the stomach, the walls of which were enormously thickened, the organ weighing 1350 grams. The cecum also was thickened, and resembled the stomach, "the greatest thickening being at the beginning of the appendix, where there is a mass 4 cm. in diameter." The solitary follicles and Peyer's patches were thickened. The appendix was firm, long and thick. There was a general slight, but definite, enlargement of all the superficial glands. The abdominal glands, especially the peripancreatic, were much enlarged, soft and pale. From the description of the microscopic appearances of the various gland groups, one has no doubt that to-day this case would unhesitatingly be called an instance of Hodgkin's disease, as it conforms to the criteria



FIG. 1.—Hodgkin's disease of the intestines, showing diffuse and localized infiltration of the intestinal wall and mesentery.

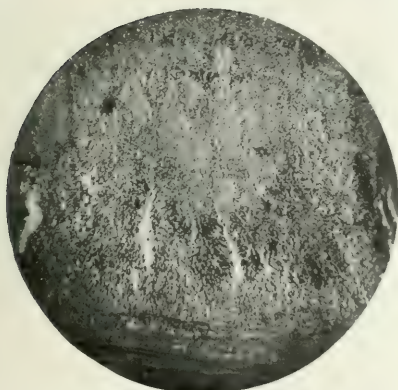


FIG. 2.—This section shows marked infiltration of the submucous and muscular layers of the wall of the intestine. (Leitz obj. 3; ocular No. 10.)

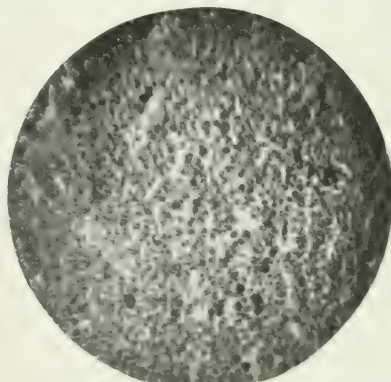


FIG. 3.—In this section are noted many endotheliocytes and endothelial giant cells in the submucosa. (B. L. obj. 4 mm.; ocular No. 10.)

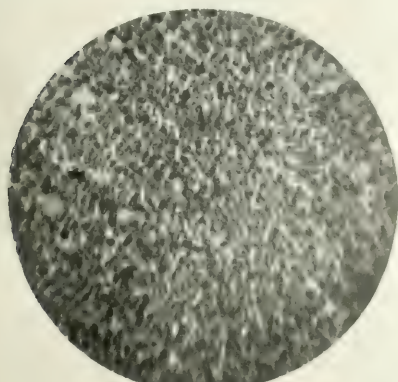


FIG. 4.—This section, through a tumor mass, shows many large cells, similar to those in figure 3. (B. L. obj. 4 mm.; ocular No. 10.)

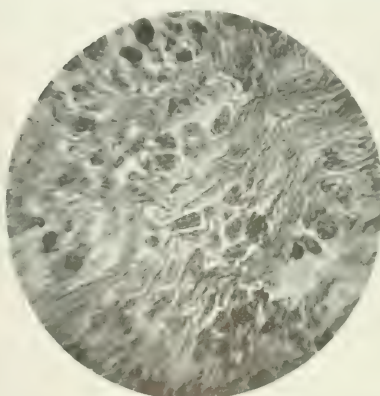


FIG. 5.—There is noted an invasion of large cells between the muscular fibers. (B. L. oil immersion 1.9 mm.; ocular No. 10.)

given by Reed, Longcope, Bunting, and others. Wells and Mayer, in their general summary, speak of their case as an instance of Hodgkin's disease.

Under the title, "Ueber einen Fall von lokalisierten Hodgkinschen Granulom der Ileocaekalklappe," Catsaras and Georgantas¹ report the case of a man 34 years old who had complained for a year of pains in the abdomen, a feeling of oppression and obstinate constipation, alternating with attacks of diarrhea. Palpation in the right iliac fossa revealed resistance and pain on pressure. The examination was, in other respects, negative.

At operation, the cecum, a large part of the large intestine, and a small part of the small intestine, were removed. The patient lived four months. He died with symptoms of dysentery and cachexia.

Examination of the tumor showed that it was submucous, the size of a mandarin orange, situated at the ileo-cecal opening. There was no ulceration: the cut section showed a homogeneous grayish-white color. The neighboring lymph-glands were slightly swollen and hard.

The histological picture was typical of Hodgkin's disease. The sections of the lymph-glands revealed similar pictures. These writers describe two kinds of giant cells: one a large cell with many vesicular nuclei; the other, a cell with dark-staining nuclei and deeply staining basophilic protoplasm. They think these latter arise from large lymphocytes. They also noted two kinds of eosinophile cells, polymorphonuclear and mononuclear. The former were found in the capillaries, the latter away from the blood channels in the tissue. They thought that the latter were lymphocytes, which had taken up the free granules of degenerated eosinophile cells.

Bunting and Yates² mention briefly the fact that in the intestines of a girl of 6 years, who died in a severe vomiting attack, the Peyer's patches of the intestines and the mesenteric lymph-nodes showed the changes of early Hodgkin's disease, which from clinical and post-mortem evidence must have been primarily intestinal in origin.

The portal of entry of the infection in our case must have been the intestine. This is most unusual. The histopathology, together with the Gram-positive bacteria in the affected tissue, seems to us conclusive evidence of Hodgkin's disease. Whether these cases are as rare as they seem to be is unanswerable at the present time. Possibly such cases have been diagnosed heretofore as lymphosarcoma or pseudo-leukemia. The present intensive study of the disease due to *B. hodgkinii* will no doubt direct attention to cases similar to this one, and assist in furthering our knowledge of this most important group.

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THE INFLUENCE OF PITUITARY FEEDING UPON GROWTH AND SEXUAL DEVELOPMENT.

AN EXPERIMENTAL STUDY.

By EMIL GOETSCH, PH. D., M. D.

Associate Surgeon, Johns Hopkins Hospital; formerly Assistant in Surgery, Harvard Medical School, and Resident Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

(From the surgical laboratories of the Harvard Medical School and the Peter Bent Brigham Hospital, Boston.)

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INTRODUCTION.

In recent years experimental and clinical observations have more and more clearly indicated a close interrelationship between the glands of internal secretion. It has been shown that alterations in function of certain of the ductless glands are accompanied or followed by changes, not only in function but in some cases in histological structure, on the part of some one or more of the remaining members of the endocrine series. One of the most striking examples of this distant change in function and structure of one gland produced by changes in another is to be seen in the alterations in the genital system consequent upon functional disturbances of the pituitary body. These alterations apply not only to primary changes in genital function, but also to the anomalies in the secondary qualities of sex. Before proceeding to a discussion of the results reported in this paper, it may be interesting to review briefly our knowledge concerning this interrelationship.

There have been recorded many clinical cases of pituitary under-function (hypopituitarism) which illustrate clearly the associated retrogressive changes in the genital system. Though Fröhlich (1901)¹ was the first to describe clearly a new clinical syndrome of adiposity and genital aplasia other than the familiar acromegaly of pituitary insufficiency, it was not until the report of experiments done in the Hunterian Laboratory by Crowe, Cushing and Homans,² that this association was demonstrated.

In this condition, which has since been called, in accordance with the suggestion of Bartels,³ *dystrophia adiposo-genitalis*, we find, in addition to the general mental and corporeal changes, marked alterations in the sex glands. In fact, the genital anomalies—in particular, disturbances of menstruation and libido—are oftentimes the inaugurating symptoms in the long series of disturbances subsequently observed.

If the pituitary insufficiency antedates puberty we find the genitals hypoplastic, one of the most striking features in the condition now known as infantilism. The secondary sex char-

acters fail to develop. In the male the body configuration is of the feminine type, the breasts are hypertrophied, there is a broad pelvis, the beard and pelvic hair are scant. Women likewise show a scant growth of pubic hair and may exhibit the masculine type of habitus with deep voice, small breasts and striking hairiness of the face and extremities.

If sexual maturity has been reached before the onset of the illness, the secondary sex characters may become retrogressive, with, for example, loss of hair of the eyebrows, of the axillæ and of the pubes. Corresponding to the retrogressive anatomical changes there is an associated diminution in function on the part of the sex glands. In females there may be a primary *amenorrhœa* or sudden *cessation of the menses* if they have previously become established, while in the males *potentia* and *libido* are poorly developed. Biedl⁴ regards the genital hypoplasias as due to deficiency of the function of the *pars intermedia*.

Another type of disease associated with disturbance in pituitary function has been recognized clinically in acromegaly and gigantism—conditions now believed by most investigators to be due to excessive activity of the gland (hyperpituitarism), contrary to Marie's first conception that acromegaly was due to its underactivity. We are acquainted with examples of excessive sexual *libido* occurring in the early stages of the disease, and with cases of premature acquisition of sexual power and secondary characteristics if the hypophysial overactivity antedates normal adolescence. One would probably find in this early active stage, were it possible to examine the sex glands microscopically, a very active spermatogenesis in the male and abundant ovulation in the female. As it is, however, the autopsy findings are concerned usually with tissues obtained after the late stage of the disease, that is, in the final period of pituitary inactivity. In this stage we find in the female cessation of menses and in the male a disappearance of the *libido sexualis*, sterility in the female, impotence in the male, and in both a high degree of atrophy of the sex glands. There are pathological changes in the spermatogenic tubules and in the interstitial cells in man, and cessation of primordial egg-formation and complete retrogression of the primordial follicles in woman. Tandler and Grosz⁵ have described these changes in greater detail.

That the pathological changes in the pituitary gland are largely responsible for these symptoms is further evidenced in the report of cases in which there has been a return of the menses and a reappearance of practically normal secondary sex characters after a decompression operation on the hypophysis or partial removal of a tumor compressing the gland and thus interfering with its function. In an analogous manner the urinary organs are affected in many instances of acromegaly. Thus, in the early stages of the disease polyuria and polydipsia are frequent symptoms; in fact this latter condition has been called a true *diabetes insipidus* and has led many to believe

¹Fröhlich, A.: Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie. Wien klin. Rundschau, 1901, XV, 883-906.

²Crowe, S. J., Cushing, H., and Homans, J.: Experimental hypophysectomy. Bull. Johns Hopkins Hosp., 1910, XXI, 127-169.

³Bartels, M.: Ueber die Beziehungen von Veränderungen der Hypophysengröße zu Misswachstum und Genitalstörungen (*Dystrophia adiposo-genitalis*). Münch. Med. Wchnschr., 1908, LV, 201

⁴Biedl, A.: Innere Sekretion, 1913, 2te Aufl., Heft II, S. 177.

⁵Tandler, J., and Grosz, S.: Die biologischen Grundlagen der sekundären Geschlechtscharaktere. Berlin, 1913, 128.

that the symptom-complex of *diabetes insipidus* is due to increased pituitary function.

The converse interrelationship—that is, a secondary pituitary change following primary alteration in the sex glands—is also illustrated by clinical and experimental conditions. Thus Compte (1898)* was the first to show that there was an increase in weight in the hypophysis at the end of pregnancy, due to hyperplasia and hypertrophy of the anterior lobe. Furthermore, Erdheim and Stumme† first demonstrated the pregnancy hypertrophy of the hypophysis in the human, and carefully described the histological changes in the anterior lobe. The essential changes in this lobe of the gland are due to the accumulation of large numbers of a new cell type—the pregnancy cell—derived from the chief cell. The eosinophiles, which normally preponderate, become much smaller and less in evidence, whereas the basophilic cells are not noticeably changed. Practically none of the normal chief cells are present. These secondary alterations in the hypophysis in pregnancy impart to the gland a very peculiar and striking appearance.

Similarly in castration, both experimentally and in the human, it has been shown that there is a consequent hypertrophy of the hypophysis. Fichera‡ was the first to demonstrate that in a series of castrated animals of different species, including the cock, ox, buffalo, guinea-pig and rabbit, there was a definite increase in the weight of the hypophysis, relatively greatly in excess of the increased growth of the animal. Histologically, in addition to the hyperæmia there was an increased number of eosinophiles. Tandler and Grosz§ were similarly able to show an hypertrophy of the pituitary body in the castrated human, as indicated by enlargement of the sella turcica, demonstrable by the X-ray in the living and by examination of the skeleton after death. Tandler|| showed that not only in Skopzen and eunuchs was there a pituitary hypertrophy following castration, but also that the same condition occurred in castrated women.

The sexual and genital changes consequent upon the production of pituitary insufficiency by experimental removal of the gland in part or *in toto* have been thoroughly studied and

observed by various investigators, this having been possible because of the comparative ease with which experimental deficiency of the hypophysis can be produced. It was first pointed out by Crowe, Cushing and Homans|| that there is a definite retarding influence exerted upon the sex glands by experimental removal of the hypophysis. In an adult dog, two years of age, a partial though extensive removal of the hypophysis was carried out. The animal seemed to become sexually impotent and a marked adiposity developed. It was sacrificed 104 days after the operation, and at autopsy there was found to be marked atrophy of the testes, with complete degeneration of spermatogenous cells and an absence of spermatozoa.

In 1912 Aschner¶ published his results of a thorough and comprehensive study of experimental hypopituitarism, showing that there is in this condition, beyond a question of doubt, marked retardation of sexual development. In brief, there is a failure of development of the testis in gross and in its histological structure. Spermatogenesis appears very late, and then is only imperfectly developed, or fails to appear at all. There is a conspicuous absence of spermatozoa. This retarded development is also observed in the penis, prostate and vas deferens. The sexual activity of such animals is reduced to a minimum. The conditions in the female are exactly analogous. In a series of similar experiments yet unpublished, I have confirmed these results, although my explanation is not in full accord with Aschner's, who attributes many of his results to operative injury of the tuber cinereum and its neighborhood during the removal of the gland. It is my opinion that the pituitary body can be removed without injury to these structures and that the failure of sexual development is due primarily to pituitary insufficiency.

Following upon these studies of hypopituitarism, attempts were made to bring about, in various ways, conditions of pituitary hyper-function, with the idea of reproducing some of the symptoms of acromegaly. In most instances these efforts failed to produce constant and positive results, at least in so far as the genital system was concerned. Von Cyon studied the effect of mechanical and electrical stimulation of the hypophysis, with especial reference to the circulation, but made no mention of the influence upon the sex glands.¶¶

The production of hyperpituitarism by the transplantation of the pituitary body has also proved to be impossible. Crowe, Cushing and Homans were the first to show that the life of totally hypophysectomized animals could be prolonged by transplantation of the hypophysis. In the partially hypophysectomized animals the development of the characteristic cachexia could thus be retarded.

Clairmont and Ehrlich|| tried to produce experimental hyperpituitarism by transplantation of the hypophysis into the spleen, but without success.

* *Loc. cit.*, p. 156.

† Erdheim, J., and Stumme, E.: Ueber die Funktion der Hypophyse. *Arch. f. d. ges. Physiol.*, CXLVII, 87.

‡ Fichera, G.: Sulla ipertrofia della ghiandola pituitaria consecutiva alla castrazione. *Policlin.*, Roma, XII, 250; also *Bull. d. v. Accad. med. di Roma*, 1905, XXXI, 91-133.

§ Tandler, J., and Grosz, S.: (a) Einfluss der Kastration auf den Organismus. *Wien klin. Wochenschr.*, 1907, (b) I. Mitteilung Beschreibung eines Eunuchenskeletts. *Arch. f. Entwickl. mechanik*, 1909, 27, 35.

|| Tandler, J.: Untersuchungen an Skopzen. *Wien klin. Wochenschr.*, 1908, S. 277.

¶ Aschner, B.: Ueber die Funktion der Hypophyse. *Arch. f. d. ges. Physiol.*, CXLVII, 87.

¶¶ Cyon, V. v.: Zur Physiologie der Hypophyse. *Arch. f. d. ges. Physiol.*, 1901, LXXXVII, 565-593.

|| Clairmont, P., and Ehrlich, H.: Ueber Transplantation der Hypophyse in die Milz von Versuchstieren. *Arch. f. klin. Chir.*, 1909, LXXXIX, 596.

* Compte, L.: Contribution à l'étude de l'hypophyse humaine et de ses relations avec le corps thyroïde. Lausanne, 1898; also, *Beitr. z. path. Anat. u. z. allg. Path.*, 1898, XXIII, 90-110.

† Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsänderung der Hypophyse. *Beitr. z. path. Anat. u. z. allg. Path.*, 1909, XLVI, 1-132.

‡ Fichera, G.: Sulla ipertrofia della ghiandola pituitaria consecutiva alla castrazione. *Policlin.*, Roma, XII, 250; also *Bull. d. v. Accad. med. di Roma*, 1905, XXXI, 91-133.

§ Tandler, J., and Grosz, S.: (a) Einfluss der Kastration auf den Organismus. *Wien klin. Wochenschr.*, 1907, (b) I. Mitteilung Beschreibung eines Eunuchenskeletts. *Arch. f. Entwickl. mechanik*, 1909, 27, 35.

|| Tandler, J.: Untersuchungen an Skopzen. *Wien klin. Wochenschr.*, 1908, S. 277.

¶ Aschner, B.: Ueber die Funktion der Hypophyse. *Arch. f. d. ges. Physiol.*, CXLVII, 87.

¶¶ Cyon, V. v.: Zur Physiologie der Hypophyse. *Arch. f. d. ges. Physiol.*, 1901, LXXXVII, 565-593.

|| Clairmont, P., and Ehrlich, H.: Ueber Transplantation der Hypophyse in die Milz von Versuchstieren. *Arch. f. klin. Chir.*, 1909, LXXXIX, 596.

Ueber den Einfluss der innersekretorischen Anteile der Geschlechtsdrüsen auf die äussere Erscheinung des Menschen. *Ber. d. Ges. f. Naturforsch.*, 1910, S. 459.

Schäfer," employing dogs, cats, apes and rats, transplanted the hypophysis subcortically, and also into the subcutaneous tissues, muscle, peritoneal cavity and kidneys, without permanent growth and healing of the graft. There was a transient polyuria, but no effect upon growth or metabolism could be demonstrated. From these and many other results the conclusion may be drawn that efforts to produce experimental hyperpituitarism by transplantation of the hypophysis are uniformly unsuccessful.

Without entering into a discussion of the physiological properties of pituitary extracts, it may be of service to mention briefly some of the effects of the administration of pituitary extract, with especial reference to its effect upon the genitourinary system.

Dale¹⁸ was the first to describe the direct stimulating action of pituitrin on the uterine musculature. Blair-Bell¹⁹ in addition described its stimulating action upon the musculature of the bladder.

Frankl-Hochwart and Fröhlich²⁰ experimented further with hypophysin, a pure extract of the posterior lobe, and confirmed and elaborated the findings of Dale and Blair-Bell. Herzberg²¹ used intramuscular injections of a similar product, "hypophysin," in cases of pregnancy, with apparently good success in causing more powerful contractions of the uterus during parturition.

Magnus and Schäfer (1901)²² and later Schäfer and Herring (1906) showed that extracts of the posterior lobe have the characteristic power of producing kidney dilatation and diuresis, especially when injected intravenously. The galactagogue action of posterior-lobe secretion, as described by Ott and Scott²³ and as further investigated by Mackenzie,²⁴ need only be mentioned, as bearing out the relationship of the pituitary body to milk secretion during and after pregnancy.

¹⁸ Schäfer, E. A.: Die Funktionen des Gehirnanhangs (Hypophysis cerebri). Berner Universitätschriften, 1911, Theil 3.

¹⁹ Dale, H. H.: On some physiological actions of ergot. Jour. Physiol., 1906, XXXIV, 163-206.

The action of extracts of the pituitary body. Bio-chem. Jour., 1909, IV, 427-447.

²⁰ Blair-Bell, W.: The pituitary body and the therapeutic value of the infundibular extract in shock, uterine atony and intestinal paresis. Brit. Med. Jour., 1909, December; also, Liverpool Med. Chir. Jour., 1910, January.

²¹ Frankl-Hochwart, L. v., and Fröhlich, A.: Zur Kenntnis der Wirkung des Hypophysins auf das sympathische und autonome Nervensystem. Arch. f. exper. Pathol. u. Pharmacol., 1910, LXIII, 347.

²² Herzberg, S.: Klinische Versuche mit den isolierten wirksamen Substanzen der Hypophyse. Deutsche med. Wehnschr., 1914, XXXIX, 1-207.

²³ Magnus, R., and Schäfer, E. A.: The action of pituitary extracts upon the kidney. Proc. Physiol. Soc., London, 1901, XXVII, 3.

²⁴ Ott, I., and Scott, J. C.: The action of infundibulin upon the mammary secretion. Proc. Soc. Exper. Biol. and Med., 1911, VIII, 48.

²⁵ Mackenzie, K.: An experimental investigation of the mechanism of milk secretion, with special reference to the action of animal extracts. Quart. Jour. Exper. Physiol., 1911, p. 305.

Borchardt (1908)²⁶ was the first to demonstrate that glycosuria could be produced in rabbits by the injection of pituitary extracts.

Many studies have been made on the effect of feeding and the injection of pituitary extracts obtained from different divisions of the gland. These studies have been directed chiefly toward the effect upon growth of the organism. The results have been strikingly contradictory. Thus, Crowe, Cushing and Homans²⁷ found that repeated subcutaneous injections of sterile extracts or emulsions of the whole gland, or of the posterior lobe alone, given subcutaneously, were apt to lead to emaciation. Caselli noted no effect on growth after long-continued injections of a whole-gland glycerin extract. Franchini (1910)²⁸ studied the effect of extracts of bovine and equine hypophysis, and particularly of extract of the posterior lobe. His conclusions are concerned chiefly with the influence upon metabolism, no mention being made of the effect upon growth or upon the genital system.

Likewise attempts have been made to simulate conditions of hyperpituitarism by feeding the fresh gland or glandular extract over long periods of time. These experiments are similarly concerned mainly with the question of growth. Caselli²⁹ believes that growth is retarded by the feeding of pituitary gland.

Sandri's³⁰ experiments in feeding young mice with bovine anterior lobe were quite negative. The feeding of posterior lobe arrested development—an effect attributed to the toxicity of the active principle.

In Schäfer's³¹ experiments with the feeding of pituitary substance (anterior lobe) to young rats there seemed to be a definite increase in the growth of those receiving the glandular extract; there was certainly no retardation of growth. More recently Aldrich,³² and similarly Lewis and Miller,³³ have reported negative results after feeding hypophysis to young rats.

Wulzen (1914)³⁴ reports retardation in the growth of young fowls by the addition to the diet of fresh, unmodified anterior lobe of the ox pituitary.

²⁶ Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie. Ztschr. f. klin. Med., 1908, LXVI, 332-348.

²⁷ Loc. cit., p. 127.

²⁸ Franchini, I.: Die Funktion der Hypophyse und die Wirkungen der Injection ihres Extraktes bei Thieren. Berl. klin. Wehnschr., 1910.

²⁹ Caselli, A.: Revista sperimentale di freniatria. Reggio-Emilia, 1900, XXVI, 176, 486.

³⁰ Sandri, O.: Archives italiennes de biologie, 1909, LI, 337.

³¹ Schäfer, E. A.: The functions of the pituitary body. Proc. Roy. Soc., 1909, LXXXI, 453.

³² Aldrich, T. B.: On feeding white rats the posterior and the anterior parts of the pituitary gland. Amer. Jour. Physiol., 1912, XXXI, No. 2, 94.

³³ Lewis, D. D., and Miller, J. L.: The relation of the hypophysis to growth, and the effects of feeding anterior and posterior lobe. Arch. Int. Med., 1913, XII, 137-144.

³⁴ Wulzen, Rosaline: The anterior lobe of the pituitary body in its relation to the early growth period of birds. Amer. Jour. Physiol., 1914, XXXIV, 127-139.

Behrenroth is the only author who makes special mention of an accompanying effect upon another of the ductless glands, produced by either the feeding or by the injection of pituitary extracts. His is the only work, furthermore, which deals with the effect of pituitary extract upon the genital system.²¹ He carried out the hypodermic administration of pituitary extract mainly for the purpose of observing its action upon the kidney, blood-pressure and metabolism. In giving the results of his investigations on the blood-pressure changes produced by pituitrin, he makes a brief statement in regard to the genital development of rats which had received hypodermically 0.2 m. doses of pituitrin.* He does not state the time during which the injections were continued, nor the derivation of the pituitrin, though it may be assumed that the extract was probably of the infundibular portion of the gland. If the injections were frequently repeated, a state of cachexia was produced, followed usually by the death of the animal. If they were given at intervals so chosen that no general disturbances were produced, the animals were usually stronger and more active than the controls of equal age. An increased growth of the skeleton was not obtained, but there was found to be a premature and extensive development of the sexual apparatus, particularly of the testes, and the animals proved to be sexually overactive. At autopsy the testes in the gross were large and hyperæmic, while microscopically they showed simply an early extensive spermatogenesis. No changes were observed in the other organs.

He observed no effect upon grown rats following administration of pituitary extract either in large doses or in often repeated small doses. In a litter of young dogs a premature sexual ripening was not obtained. Behrenroth is at a loss to explain the variability in these results. A possible explanation may be a difference in the activity of the extracts, or a failure in some cases to administer the correct amount necessary to produce a stimulating effect. Only slight changes were observed in the female animals. His series is a small one, the microscopical report is very limited, and in the original work no drawings or diagrams are given. We shall have occasion to return to these results.

From this brief review of the literature it can readily be seen that both experimentally and clinically there is a direct interrelationship between disturbances in the genito-urinary sphere and affections of the pituitary body. The normal hypophysis seems without doubt to exert a stimulating influence on the development and activity of the genital organs. Excessive activity of the gland is followed by premature development and overactivity of the genital organs; its deficient function results in genital underdevelopment and the non-appearance of sex characteristics. Previous suggestions on the part of other investigators, and almost certainly our own results, would indicate that it is the anterior lobe of the hypophysis which exerts this specific influence upon the sex glands.

The idea is an old one that a deficiency in the secretion of any one of the ductless glands can to large measure be overcome by administration of the extract of the gland in question. The administration of glandular extract by mouth, hypodermically, intravenously and intraperitoneally, has been carried out both clinically and experimentally, and undoubtedly in many instances much benefit is obtained; for example, in experimental hypopituitarism in the dog, prolongation of life and a more nearly normal development have followed the administration of pituitary extract, and similarly in clinical conditions beneficial results have been obtained. Empirical feeding and other forms of glandular administration have also been practised in conditions of thyroid and ovarian deficiency, but with results never quite under the control of the observer and not capable of close analysis and test. Thus, so far as I am aware, no histological evidence has ever been given of any effect upon either of these glands or upon any other of the ductless glands, produced by administration of gland extracts, and consequently we have only subjective symptoms and more or less indefinite and uncertain objective signs and manifestations to indicate the result of our therapy. Reference should be made here to the splendid work of Gudernatsch²² and to the very definite results he has obtained by feeding thyroid and thymus extract to young tadpoles. In his experiments thyroid extract had the effect of producing very early and rapid development of the young tadpole into a miniature frog, whereas thymus extract had no such stimulating action upon differentiation, but on the contrary produced overgrowth of the young tadpole into a giant tadpole. No reference is made to the effect upon the individual ductless glands.

This research is based on the conception that if hypopituitarism results in retardation or cessation of body and reproductive development, then one may expect increased growth and increased rapidity of sexual development from the administration of pituitary extract. Interest was aroused in the possibility of producing over-development and activity in the sex glands by the feeding of pituitary extract during the course of some experimental work done in the Hunterian Laboratory six years ago. Preliminary studies were carried out on the effect of anterior-lobe feeding upon growth and development. Two young female dogs of the same litter were taken; to one of these, dried extract of anterior lobe was given in daily doses of 0.5 gm. The second female was used as a control. At the end of about 7 months of this feeding the animals were sacrificed, and in the routine examination of the ductless glands it was found that the ovary of the animal receiving the anterior lobe extract contained numerous corpora lutea and corpora albicantia, whereas in the control animal the ovary contained simply the unripe Graafian follicles not yet mature enough for the occurrence of ovulation. Here was a hint which gave encouragement for more thorough investigation of this subject, which was begun three years

²¹ Behrenroth, Erich: Ueber die Einwirkung des Hirnanhangsextraktes auf den Blutdruck des Menschen nebst Bemerkungen über einige Injektionsversuche am wachsenden Tier. Deutsch. Arch. f. klin. Med., CXIII, 393-395.

²² Gudernatsch, J. F.: I. Feeding experiments on tadpoles. Arch. f. Entwicklungsmech. u. Organ., 1912, XXXV, 457. II. A further contribution to the knowledge of organs with internal secretion. Am. Jour. Anat., 1914, XV, 431.

ago. It is the purpose of this report to give the results of pituitary feeding in young rats, with especial reference to the early development and the histological changes produced in the sex apparatus and to its influence on breeding and parturition. In this report the facts in regard to the effect upon growth will be considered only in a general way.

METHODS OF STUDY.

Young rats were used in these experiments, in the first place, because they are hardy animals and their active sexual life and development, as well as their breeding habits, can be readily observed even under the somewhat abnormal environments of laboratory experimentation; and, in the second place, because it was thus possible to obtain young animals of pure breed and known pedigree and to avoid in this way the possibility of variations in body growth as well as in genital development in different members of the same litter—a possibility which might arise in case the animals were of mixed parentage. In our experiments the members of the different litters when weaned varied in weight, size and general appearances only to a negligible degree, the variation in weight in many instances being merely a fraction of a gram. Where there was an appreciable difference, the odds were usually taken by the experimenter in choosing the animals to be fed and those to be used as controls. The animals were used as soon as weaned, their ages at the time varying between $3\frac{1}{2}$ and 4 weeks.²² They were placed in wire cages, of double size for pairs, with an abundant supply of fresh water. The food consisted of cracked grain (corn, barley and seed) and white bread soaked in rich milk, given in definite amounts daily to each rat. The amount of grain was so calculated that there was always some remaining in the cage on the day after feeding. At the beginning of the experiments only cracked grain was given, but as it was apparent that the animals were not developing or increasing in weight satisfactorily, the bread-and-milk diet was added, with a consequent rapid growth. Dried powdered extract of bovine anterior and posterior lobe, separately and in combination, was used. In each experiment controls were taken from the same litter and were kept under precisely similar conditions without glandular administration or with control-feeding of ovarian or corpus luteum extract.²⁴ At first 0.1 gm. and later .05 gm. of the powdered extract (anterior, posterior and combined lobes) was given daily in a pill of bread and milk. The extract was given in pill form in order to insure each animal's receiving the quota desired. Thus when two animals occupied the same cage the experimenter could be sure that each received the same amount. The animals ate the pills greedily, and thus no difficulty was experienced in administering the extract. In

several instances ovarian or corpus luteum extract in equal amounts was given to the control animal, to offset the effect, if any, of the feeding of the pituitary extract itself. However, as the material is fed in such small amounts this objection is practically negligible.

At the beginning of the experiment, for a period of about 12 days, 0.1 gm. of the extract was given. Under this dosage, however, the animals did not gain satisfactorily in weight; there was loss of appetite and a tendency to diarrhea, due undoubtedly to overdosage, and consequently the amount was decreased to .05 gm., or half the original dose. The feeding was continued over different lengths of time, varying from 12 days to 6 or 8 months. During this period frequent observations were made on the growth and weight of the animals and upon the development of the genitals and nipples. At the end of the experiments the ductless glands were preserved in fixatives and embedded in paraffine. Sections were cut, 5μ in thickness, stained usually in hæmatoxylin and eosin, and compared. The technical procedure was kept absolutely the same for the fed animals and the controls. Some of the earlier experiments were interrupted because of a peculiar snuffles and bronchopneumonia which developed among the rats, causing their almost immediate death. In no case was an animal which had shown any previous signs of decline or disease included in the final results. In a few instances pairs of rats of the same litter were selected, one pair being fed anterior-lobe extract, the other being used as a control; observations were then made on breeding, time of parturition and the size and weight of the litters. In these few cases interesting comparisons can be made on the effects of feeding anterior- and posterior-lobe extracts. In other words the conditions of experimentation were made as nearly as possible the same for all the animals under observation.²⁵

EXPERIMENTAL RESULTS.

In reporting the experimental findings it is thought best to give a condensed account of each protocol in tabular form instead of the complete protocol of each case. Many of the findings, especially those relative to weight and growth and to the histological changes in the ductless glands other than the sex glands will be reserved for a later report. First, it may be of interest to record some of the more acute experiments—those intended to show the effect of whole-gland feeding (anterior and posterior lobes, including the intermediary portion) over a brief period of time. For this purpose the record of two female rats of Litter IV will be given.

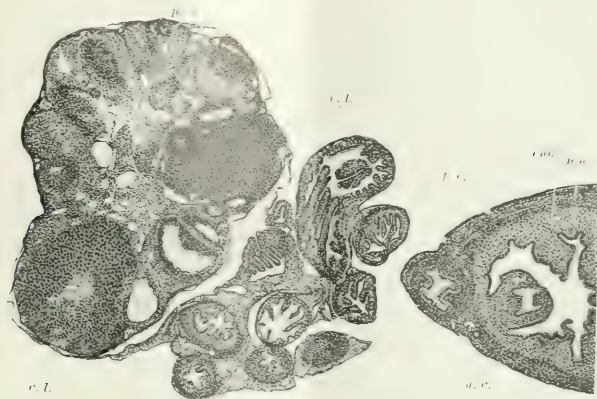
THE EFFECT OF FEEDING PITUITARY EXTRACT (WHOLE GLAND) OVER A BRIEF PERIOD TO A YOUNG FEMALE RAT.

LITTER IV.—Litter of black rats, 3 males and 2 females. Born Feb. 10, 1913; weaned at the age of 4 weeks. Glandular feeding (whole gland, consisting of equal parts by weight of the dried powdered extract of the anterior and posterior lobes) begun to

²² It is a pleasure to express here my gratitude to Dr. W. E. Castle of the Bussey Institution, Harvard University, Boston, for his kindness in furnishing the experimental animals used in this work and for his helpful suggestions in regard to their care and feeding.

²⁴ I wish to express here my appreciation of the kindness of Mr. Charles M. Bell, of the Armour Laboratories in Chicago, in furnishing the pituitary extract used in these experiments.

²⁵ In so far as I am aware, these are the first observations to be made on histological changes produced in any of the ductless glands by the oral administration of pituitary extract.

FIG. 1.—Female I (pituitary fed). $\times 26$.FIG. 2.—Female II (control). $\times 26$.

Figs. 1 and 2 represent in one plane the ovary, the fimbriated end of the tube and the beginning of the uterine cornu of two young rats, 2½ mos. old, of the same litter, to the first of which, Fig. 1, Female I) pituitary extract (whole gland) was given over a period of 42 days, from the time when the animal was 30 days old; the second, the control (Fig. 2, Female II), received no glandular feeding. Both animals were sacrificed when they were 72 days, or 2½ mos. old. Compare, in Fig. 1, the presence of corpus luteum (*c. l.*), the scarcity of unripe follicles (*u. f.*), the marked endometrial hyperplasia in the uterine cornu (*u. c.*), the proliferation of the fimbriated end of the tube (*f. c.*), and the increased vascularity in the hilus of the ovary (compare Fig. 2) the number of unripe Graafian follicles (*u. f.*); the absence of primordial follicles, the smaller degree of branching of the fimbriated end of the tube, and the simple thin mucous membrane in the uterine cornu (*u. c.*) and the primordial follicles. *End.*—Endometrium, *m. m.*—myometrium.

Female I, March 12, when the animal was 30 days old. Female II used as control. At first 0.1 gm. was given daily; but as this dose was found to be too large (the animal failed to gain in weight, and there was loss of appetite and a tendency to diarrhoea), after 10 days it was reduced to .05 gm., and this amount was given for the following 32 days, the feeding thus lasting altogether for 42 days. At the beginning of the experiment, Female I weighed 27.6 gms., 3.4 gms. more than the control. At the end of the observation the weight of Female I was 93.5 gms., as compared with 81.9 gms., the weight of the control—a rather remarkable gain in so short a time. Both animals were autopsied on April 22 at the age of 72 days, or 2½ months. Besides the definite gain in weight, the nipples were larger and more conspicuous in Female I, the animal receiving the whole-gland feeding (cf. protocol).

TABLE I. CONDENSED PROTOCOL.
LITTER IV.

Date.	Female I. Whole-gland feeding for 42 days.	Female II. Control. No gland administration.
Mar. 11.	Weight, 27.6 gms.	Weight, 24.2 gms.
Mar. 18.	Weight, 31.2 gms.	Weight, 25.8 gms.
Mar. 31.	Pectoral nipples fairly large.	Nipples fairly prominent.
Mar. 31.	Weight, 60.3 gms.	Weight, 59.0 gms.
Apr. 13.	Weight, 77.9 gms. Large, conspicuous nipples. Animal large, active, inclined to be vicious.	Weight, 72.2 gms. Nipples small. Hair fairly thick.
Apr. 22.	Autopsy Weight, 93.5 gms. Generally larger animal as compared with control. <i>Uterus</i> and <i>ovaries</i> definitely larger than in control; both of the latter thicker and have an edematous-swollen appearance as compared with control. <i>Corpora</i> slightly smaller than in Female II. Two or three yellowish granules seen—probably corpora lutea.	Autopsy Weight, 81.9 gms. Fur smoother and more delicate than that of Female I (fed animal). <i>Uterus</i> , <i>cornea</i> and <i>ovaries</i> definitely smaller than in Female I. <i>Ovaries</i> contain two or three small, yellowish granules resembling in appearance those in ovaries of Female I, and in addition several glistering bodies, possibly Graafian follicles.

Nothing of special note concerning the other ductless glands of gross examination.

By comparison of the condensed tabulated protocol of the fed animal with that of the control, the following points become apparent. The animal fed with pituitary whole-gland extract (Female I) developed more rapidly than the control, as shown by the final weight. The nipples were noticeably larger than those of the control, and the hair possibly coarser. Furthermore, at autopsy the body of the uterus, the *cornea* and ovaries were found to be definitely larger and more vascular and edematous than those of the control, and the ovaries of the fed animal contained what appeared in gross, and on examination proved to be, corpora lutea, which were conspicuously absent in the ovaries of the control animal.

Microscopic.—Both ovaries, the *cornea* and the body of the uterus in each case were fixed in Carnoy's solution. Sections were made at different levels in the *cornea*. Comparison of these sections from corresponding levels showed the differences between Female I and Female II as those illustrated in Figs. 3 and 4. Serial sections were also made at short intervals through the entire ovaries in order to find missing possible Graafian follicles or corpora lutea at different levels. For purposes of comparison the ovary was so mounted that a section through its center included the fimbriated extremity, the tube and the beginning of the *cornea* (Figs. 1 and 2).

A comparison of the low-power drawings of the ovary of Female I (whole gland feeding) with those of the ovary of Female II (control) shows the following differences. Even at the early age of 24 months the ovary of the pituitary-fed animals (Fig. 1) shows the presence of corpora lutea (cf. Fig.), which are conspicuously absent in the ovary of Female II. In fact, in the latter we find numerous primordial follicles (*p. f.*) and a number of young unripe Graafian follicles (*u. f.*). There are very few primordial follicles in the ovary of Female I (Fig. 1, *p. f.*); it shows increased vascularity in the medulla and hilus; the fimbriated end (Fig. 1, *f. e.*) of the tube is more extensively divided; the folds of mucous membrane are very much higher, and with the high power magnification one sees that the lining columnar cells are considerably taller and more uniformly ciliated. Furthermore, the uterine cornu (*u. c.*), the end of which is represented in Figs. 1 and 2, shows a marked hypertrophy and hyperplasia of the mucous membrane lining (endometrium, *end.*) and an increased thickness of the muscular coats (myometrium, *my.*), together with an increased vascularity, the latter being particularly noticeable in the high-power study. All these findings are characteristic of the sexually mature female genital system.

Figs. 3 and 4 illustrate the difference between the uterine cornu of the pituitary-fed animal, Female I, and that of the control, Female II. These sections were taken from the mid-points of the cornua, but similar differences were observed at other corresponding points. In Fig. 3, as compared with Fig. 4, the striking differences are: The marked hypertrophy and hyperplasia of the mucous membrane (endometrium, *end.*), with the formation of uterine glands (*u. g.*)—a condition resembling the change occurring in pregnancy; the increased thickness of the muscle coats (myometrium, *my.*); and the increased vascularity. (Note the simple structure of the uterine cornua in the control animal.)

A comparison of Figs. 5 and 6 shows these differences to an even greater extent. The sections, here taken at the junction points of the uterine cornua, indicate that an even more marked change has taken place in the body of the uterus of the pituitary-fed animal than is represented in the cornua (Fig. 3). The lining cells of the uterine mucosa are taller and richer in protoplasm, and are supplied more uniformly with cilia, in the fed animal than in the control.

In view of the marked changes produced by the feeding of pituitary extract to the young female rat, we are warranted in saying that the extract caused early and extensive ovulation, marked growth and indications of activity on the part of the fimbriated end of the tube, and a marked hypertrophy and hyperplasia of the uterine mucosa. These changes were entirely absent in the control animal. When we consider that they appeared at the early age of 24 months, whereas normally they should occur between the ages of 3 and 4 months, and even then less extensively—we have undoubted proof of the extremely selective and almost specific action of pituitary extract upon the genital system.

ON THE COMPARATIVE EFFECTS OF THE FEEDING OF PITUITARY WHOLE-GLAND, POSTERIOR-LOBE, AND OVARIAN (CORPUS LUTEUM) EXTRACT. COMPARISON OF CONDITIONS IN A CONTROL RECEIVING NO GLANDULAR EXTRACT.

Four male rats from Litter II were used in this experiment. In the litter, born February 6, 1913, there were 7 young, 3 pairs and one single male. The animals were of the same breed, narrow selection series, and of the same variety of gray rat (*Mus Norvegicus*). The young rats were weaned on March 5, when 27 days, practically 4 weeks, old, and were

until April 12, when the animal was sacrificed. The feeding was continued altogether for 36 days. Age at autopsy, 65 days.

A final comparison of the four male rats unfortunately cannot be made, as the period of feeding and the ages of the animals at autopsy were not the same in each case. However, comparative observations were constantly made at different periods during the feeding and are of considerable interest. They are summarized in the following protocols:

Male, Pair I (whole-gland feeding).—The testes remain descended at an earlier period than in the control (male, Pair III, cf. March 12). The weight of the right testis at autopsy, at the

TABLE II.—CONDENSED TABULATED PROTOCOLS OF MALES OF LITTER II, TO SHOW THE COMPARATIVE EFFECTS OF FEEDING PITUITARY WHOLE-GLAND AND POSTERIOR-LOBE, AND OVARIAN EXTRACTS. FEEDING BEGUN WHEN ANIMALS WERE FOUR WEEKS OLD.

Date.	Male, Pair I. Whole-gland feeding, 16 days. Age at autopsy, 44 days.	Male, Pair II. Ovarian feeding, 34 days. autopsy, 65 days	Age at	Male, Pair III. Control. Age at autopsy, 59 days.	Single Male. Posterior-lobe feeding, 36 days. Age at autopsy, 65 days.
Mar. 5.	Weight, 29.7 gms.	Weight, 30.4 gms.		Weight, 29.4 gms.	Weight, 30.5 gms.
Mar. 12.	Testes descended. External genitalia prominent.	Testes descended, of good size; can be readily slipped back into abdomen.		Testes descend when rat is on all fours. When rat is picked up, testes enter abdomen.	Testes descended. Remain outside at all times. External genitalia (penis) of fair size.
Mar. 18.	Has lost some weight, due to too large a dose of extract. In good condition. Good coat of fur of delicate texture.	Testes at times in abdomen; can readily be expressed downwards.		Testes have a tendency to return to abdomen.	Testes descended; of generous size.
Mar. 22.	Found dead in cage this a. m. No apparent cause. Seemed well on previous day. Possibly too large a dose of extract. Slight enteritis.	No Large testes and scrotum looks vigorous.	Animal	Testes not descended at all times. Not a vigorous animal.	Testes and scrotum large by comparison with control male. Slight enteritis.
Autopsy.					
	Congestion of lungs. Testes quite large, on gross examination, for rat of this age. Weight of right testis, 0.260 gm. Nothing of special note revealed by autopsy on gross examination.				
Mar. 30.		Testes fairly large. Tremor noticeable in feet, also of whole body.		Testes not as large as in single male (posterior-lobe feeding), nor quite so large as in ovarian-fed animal. No tremor of limbs.	Rat large and vigorous. Testes and scrotum large and of greater size than those of control. A fairly marked tremor of legs and body.
Apr. 6.				Weight, 54.3 gms. Found dead in cage this a. m. Externally nothing unusual. Scrotum and penis small. Weight of right testis, epididymis and vas, 0.260 gm. Weight of left testis, epididymis and vas, 0.270 gm.	Weight, 51.2 gms. Testes slightly larger than in ovarian-fed animal (male, Pair II).
Apr. 12.		Weight, 89.7 gms. Well grown, fat, lively and in good condition. Sacrificed. Weight of right testis, epididymis and vas, 0.870 gm. Weight of left testis with epididymis, 0.860 gm. Weight of both seminal vesicles, 0.340 gm. Seminal vesicles large and tortuous. Testes slightly larger and harder than those of posterior-lobe-fed male. Fur heavier and slightly coarser.			Weight, 83.7 gms. In very good condition; well grown, not especially adipose. <i>Sacrificed.</i> Weight of right testis, epididymis and vas, 0.740 gm. Weight of left testis, epididymis and vas, 0.730 gm. Seminal vesicles, 0.330 gm. Testes smaller on palpation and inspection than in ovarian-fed rat (male, Pair II).

separated into three pairs and one single male, each pair and the single male being placed in different cages.

Male, Pair I, received whole gland extract (anterior and posterior lobes, 0.05 gm. of each) for 16 days, from March 6 to March 22. The feeding was continued altogether for 16 days. Age at autopsy, 44 days.

Male, Pair II, received 0.1 gm. ovarian extract (corpus luteum, Parke, Davis & Co.) for 14 days, beginning March 9; then 0.05 gm. daily for the following 29 days, until April 12. The feeding was continued altogether for 43 days. Age at autopsy, 65 days.

Male, Pair III, used as a control. Died suddenly April 6. Age at autopsy, 59 days.

Single male received 0.1 gm. posterior-lobe extract for 15 days, beginning March 7; then 0.05 gm. for the following 21 days, or

age of 44 days, is the same as the weight of the right testis of the control animal (0.260 gm.) at the age of 59 days. One tenth of a gram daily, both of whole-gland and of posterior-lobe extract, proved to be too large a dosage (cf. March 22).

Male, Pair II (ovarian feeding).—There is no difference in the period of permanent descent of the testes as compared with that in the control animal (cf. March 12). There is a tendency toward the deposition of fat and a marked increase in weight—as shown at autopsy, an increase of 6 gms. over the animal fed with posterior-lobe extract (cf. April 12). The fur of the animal fed with ovarian extract is heavier and slightly coarser than that of the animal fed with posterior lobe (cf. April 12). The testes are slightly heavier (0.1 gm.), but this may be due rather to an inhibitive effect of the posterior-lobe extract than to a stimulating effect of the ovarian extract (cf. April 12).

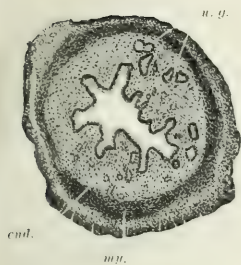


FIG. 3.—Female I (pituitary fed). $\times 31$.

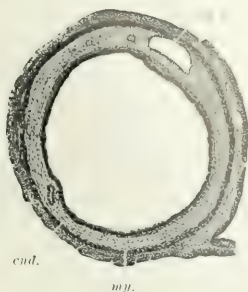


FIG. 4.—Female II (control). $\times 31$.



FIG. 6.—Female II (control). $\times 32$.

Figs. 3 and 4 represent transverse sections through the middle of the right uterine cornua of the same young rats whose ovaries are represented in Figs. 1 and 2.

Fig. 3. Section from the uterine cornu of the female to which pituitary extract (whole gland) was given over a period of 42 days, from the time when the animal was 30 days old.

Fig. 4. Corresponding section from the control female who received no gland extract.

Note in the endometrium (*end.*) the marked hypertrophy and hyperplasia of the uterine mucosa with active gland formation (*u. g.*) suggesting the pregnancy reaction, the very cellular character of the propria, and the increased thickness of the musculature of the myometrium (*my.*).

Figs. 5 and 6 represent transverse sections through the junction points of the uterine cornua (cervix uteri) of the same rats, whose ovaries and cornua are represented in Figs. 1, 2, 3 and 4.

Fig. 5. Section from the cervix of the uterus of Female I, to which pituitary extract (whole gland) was given over a period of 42 days from the time the animal was 30 days old.

Fig. 6. Section taken from the control animal at a point corresponding to that represented in Fig. 5.

The histological differences in Figs. 5 and 6, are similar to, but even more marked, than those represented in Figs. 4 and 5.



FIG. 5.—Female I (pituitary fed). $\times 32$.

Male, Pair III (control animal without glandular administration).—The tendency for the testes to return to the abdomen persisted longest in this animal (*cf.* March 22). On gross palpation they are smaller than the testes of any of the other animals (*cf.* March 22). The weight of the right testis of the control is the same as that of the animal fed with whole-gland extract, though the former animal was two weeks older than the latter.

Single Male (posterior-lobe feeding).—The testes permanently descended at an earlier period than those of the control (*cf.* March 18). On palpation they were larger. At autopsy the animal weighed less than the ovarian-fed animal (*cf.* April 12), and the weight of the testes was also less.

Briefly summarized, the main differences that may be observed from the protocols are as follows:

Posterior-lobe feeding, as compared with the feeding of ovarian extract, does not produce a stimulating effect on the growth of the body or testes. Whole-gland feeding increases the growth of the testes as compared with those of a control animal. Ovarian extract has a tendency to cause the deposi-

COMPARISON OF ANIMALS RECEIVING WHOLE-GLAND FEEDING AND OVARIAN FEEDING WITH A CONTROL RECEIVING NO GLANDULAR EXTRACT.

Three female rats from Litter II, the mates of the three paired males of the preceding table, were used for this experiment. Two of the animals died suddenly of snuffles; the third was sacrificed. They were of the same age at the time of autopsy, which was carried out immediately. The two animals dying of snuffles had been in good condition up to within a day or two of death. The third animal was entirely well.

Female, Pair I, received 0.1 gm. pituitary whole-gland extract (anterior and posterior lobe in equal parts) for 16 days, then 0.05 gm. for the following 8 days. Total period of feeding, 24 days. Age at autopsy, 53 days.

Female, Pair II, received 0.1 gm. of ovarian (corpus luteum) extract for 13 days, then 0.05 gm. for the following 10 days. Total period of feeding, 23 days. Age at autopsy, 53 days.

Female, Pair III, used as control, with no glandular administration. Age at autopsy, 53 days.

TABLE II CONTINUED.—A COMPARISON OF THE HISTOLOGICAL APPEARANCE OF THE TESTES OF FOUR MALE RATS OF LITTER II, THREE OF WHICH RECEIVED RESPECTIVELY WHOLE-GLAND, OVARIAN AND POSTERIOR-LOBE FEEDING, THE FOURTH BEING USED AS A CONTROL.

Male of Pair I. Whole-gland feeding, 16 days. Age at autopsy, 44 days.	Male of Pair II. Ovarian feeding, 34 days. Age at autopsy, 65 days.	Male of Pair III. Control. Age at autopsy, 59 days.	Single Male. Posterior-lobe feeding, 36 days. Age at autopsy, 65 days.
<i>Testis:</i> No spermatozoa present. Karyokinesis quite active, but only in its early stages. Development has reached the stage of the spermatocytes of the first order. No spermatids present. Majority of the tubules lined with 2 or 3 rows of cells, in places with 4 rows.	<i>Testis:</i> Spermatozoa present in fairly good numbers, though not as numerous as one would expect from the degree and extent of karyokinesis present. The majority of the tubules are at the spermatid stage and contain a great amount of secretion.	<i>Testis:</i> No spermatozoa present. Karyokinesis quite well advanced, but only to the spermatocyte stage and hardly as far as in the case of the male of Pair I (whole-gland feeding), although the latter is 15 days younger. Tubules contain a small amount of secretion.	<i>Testis:</i> Spermatozoa just beginning to become conspicuous in certain of the tubules. These latter are mostly in the spermatid stage at least. Karyokinesis quite active, though possibly somewhat less far advanced than in the male of Pair II (ovarian feeding). The cells are more protoplasmic.
<i>Interstitial cells</i> few.	<i>Interstitial cells</i> fairly numerous and present in larger numbers than in testis of the male of Pair I.	<i>Interstitial cells</i> few. No specially noticeable difference from male of Pair I.	<i>Interstitial cells</i> fairly abundant and large. Connective tissue fairly perceptible.
<i>Epididymis</i> lined with tall, full cells, mostly ciliated.	<i>Epididymis</i> lined with a lower type of columnar cells, not so regularly ciliated. Lumina of the tubules somewhat wider and containing some few spermatozoa and here and there a few free cells. A good deal of vacuolation in the tubular cells and between them, possibly due to the disappearance of fat or lipidal substance.	<i>Epididymis</i> not examined.	<i>Epididymis:</i> Cells stain well, have abundant protoplasm, of medium height, ciliated. Some secretion and a few free cells in lumina. No spermatozoa seen. Very little secretion in the tubules.

tion of fat and a coarser growth of hair. The histological appearance of the testes of these four rats, illustrating the effect of different gland feeding, is indicated in the accompanying table.

From this table, as far as comparison can be made, after allowing for the differences in the ages of the animals, the following facts may be deduced. The feeding of whole gland to the male of Pair I caused an appearance of development of the testes as far advanced as in the control animal, although the latter was 15 days older. No especial effect upon the interstitial cells was noted.

There was little difference in the effect of ovarian and posterior-lobe feeding on the male of Pair II and the single male respectively. Neither extract seemed definitely to stimulate testicular development, but on the contrary appeared to retard it. This effect was possibly more definite in the ovarian-fed animal. Not only over the whole body, but also in the testis of the ovarian-fed animal there was a tendency toward the deposition of fat.

From a consideration of Table III it will be seen that whereas, at the beginning of the experiment, the rat which received whole-gland feeding was the lightest in weight, at the end, after 24 days of feeding, it weighed more than either of the others. Next in weight at the end of the experiment was the ovarian-fed animal. There is an indication here of the stimulating influence on growth of whole-gland extract. There is also seen to be a tendency toward the production of slight diarrhoea, muscular tremors, nervous manifestations and weakness of the hind legs by the feeding of too large a dose of the whole-gland extract; and it was for this reason that the dose of pituitary extract was decreased, as in other experiments to be reported later. None of these symptoms, except tremor, were apparent in the ovarian-fed animal, and they were not observed in the control.

The effect of glandular feeding was apparent even in the nipples. These were most conspicuous in the rat receiving whole-gland extract, and were very small and inconspicuous in the control. This increase in development of the nipples is a

TABLE III.—CONDENSED TABULATED PROTOCOLS OF THE THREE FEMALES OF LITTER II, FED ON (1) WHOLE-GLAND AND (2) OVARIAN EXTRACT, AS COMPARED WITH ONE ANOTHER AND WITH (3) A CONTROL WITHOUT ANY GLANDULAR ADMINISTRATION.

Date	Female, Pair I. Whole-gland feeding, 24 days. Age at autopsy, 52 days.	Female, Pair II. Ovarian feeding, 23 days. Age at autopsy, 53 days.	Female, Pair III. Control. No glandular administration. Age at autopsy, 53 days.
Mar. 5.	Weight, 28.2 gms.	Weight, 28.7 gms.	Weight, 30.1 gms.
Mar. 12.	Internal genitalia small and white.	No difference in appearance of external genitalia.	No difference in external genitalia.
Mar. 23.	In good condition. Slight diarrhea. Not a vigorous animal. Nipples fairly easily distinguishable.	Nipples just distinguishable with ease. No diarrhea.	Nipples just visible. No diarrhea. Smaller than either the female of Pair I or the female of Pair II.
Mar. 30.	Died suddenly. Very remarkable fine tremor in practically all the muscles. Heart-beat strong, respirations and pulse rapid. Weakness of hind legs. Weight, 57.5 gms.	Weight, 56.9 gms. Nipples not readily visible, and slightly smaller than in the female of Pair I. Tremor in feet and body also well marked.	Weight, 54.2 gms. Nipples fairly easily seen. Absolutely no tremor apparent or felt in muscles of body generally.
	Autopsy.		
	Ovaries fairly large, with apparently a definite mass of Graafian follicles, translucent in appearance.		
	Ovaries, tubes and uterus preserved in Carnoy's solution.		
Apr. 1.	No enteritis present.	Found dead in cage this a. m. Appeared to be well on previous day. No external features of special note. Ovaries, tubes and uterus preserved. Nothing striking on gross examination. Graafian follicles less conspicuous than in the female of Pair I. Ovary and uterus of fair size; larger than in control and possibly slightly larger than in animal fed with whole gland.	Killed by mate. Ovaries, tubes and cornua of uterus noticeably smaller than in the females of Pairs I and II.

rather remarkable effect of pituitary feeding over so short a period.

Examination of the ovaries, tubes and uteri in the gross showed that they were farther developed in Females I and II, the animals fed with glandular extract, as evidenced by the definite mass of Graafian follicles in the ovaries and by the larger size of the uteri of these two animals. There is no doubt that here both whole-gland and ovarian feeding had a stimulating effect upon ovarian and uterine development. The ovarian extract was equally as stimulating in this respect as the whole-gland extract—a fact due in all likelihood to the small amount of anterior lobe contained in the dosage of whole gland that was administered, for it would seem that it is the anterior lobe which is responsible for the stimulating action. The posterior-lobe element seems without doubt to have rather an inhibitive action in this regard. Further evidence in support of this view will be given later.

We come now to a comparison of the histological findings in the ovaries, tubes and uteri of the three female rats (*cf.* Table IV).

By comparing the histological appearance of the ovary and tube in each animal, as given in the above table, it is apparent that the whole-gland extract and the ovarian extract have exerted a stimulating effect upon the development of these organs. In evidence of this we find a strikingly greater number of well-developed Graafian follicles and a small number of primordial follicles in the case of the animals fed with whole-gland and with ovarian extract, as compared with the control. The small number of primordial follicles present in the former would indicate that a great many have undergone development and are approaching maturity, whereas in the control most of them are still dormant. Corresponding to the greater ovarian development, as indicated by the developing follicles, there is an accompanying moderate increase in the amount of interstitial tissue. The reaction is not confined to the ovary, for in

TABLE IV.—HISTOLOGICAL COMPARISON.

Female, Pair I. Whole-gland feeding, 24 days. Age at autopsy, 52 days.	Female, Pair II. Ovarian feeding, 23 days. Age at autopsy, 53 days.	Female, Pair III. Control. No glandular administration. Age at autopsy, 53 days.
Ovaries: Fairly large, and in each a definite mass of Graafian follicles seen in gross; translucent in appearance. Microscopic examination shows a moderate number of developing follicles and a few unripe primordial follicles. No corpora lutea.	Ovaries: A large number of well-developed Graafian follicles, a considerable number beginning to develop, and a few primordial follicles.	Ovaries: A moderate number of Graafian follicles not far developed. A large number of primordial follicles with no sign of development in marked contrast with Female I (whole-gland feeding) and Female II (ovarian feeding).
Interstitial tissue fairly rich.	Interstitial tissue rich.	Interstitial tissue less in amount than in ovary of Female I and ovary of Female II.
Fimbriated ends of tubes lined with compact, tall, ciliated columnar cells.	Fimbriae of tubes lined with tall, folded columnar epithelium, which is fairly uniformly ciliated.	Fimbriae lined with cells not especially large or active in appearance, in contrast with conditions in the two other animals. Considerable folding of mucous membrane; cells mostly ciliated.

the case of the two animals that received glandular extract there is a greater branching of the fimbriated ends of the tubes, a taller epithelial lining and a more complete ciliated lining of the cells. These are evidences of activity on the part of the tubes. In this respect ovarian extract seems to be equally as stimulating as whole-gland extract.

THE EFFECT OF ANTERIOR-LOBE FEEDING ON THE YOUNG MALE RAT.

Two male rats of Litter III, of pure breed, were taken for this comparison, one being fed anterior-lobe extract and the other being used as a control without glandular administration. In this litter there were five young, two pairs and one single male. Pair I were given posterior-lobe extract, Pair II were used as controls, and the single male received anterior-lobe extract.

The protocol of the animal fed with posterior lobe will not be recorded here, and for purposes of comparison, we shall give briefly the protocols of only two of the animals used in this experiment, to show the stimulating effect of anterior-lobe feeding upon testicular development, when these animals are compared with a control without glandular administration.

Male, Pair II, used as a control without glandular administration. Died, April 24. Age at autopsy, 71 days.

Single Male I, received daily 0.1 gm. of anterior-lobe extract (Armour & Co.), beginning March 9, at the age of 25 days, and continued for 14 days. Fearing that the dose of glandular extract was too large, 0.05 gm. of the extract was given for the following 71 days. The animal was sacrificed June 15. Total period of feeding, 85 days. Age at autopsy, 123 days.

During the course of the experiment the right testis was removed surgically from each animal. This was done on April 18, when the animals were 65 days old. The purpose of the procedure was to obtain a comparative observation on the testes of the two animals at a definite time during the course of the experiment, and by preserving the animals' lives to make another observation on the remaining testes after a considerably longer period of feeding had elapsed. The testes thus removed were weighed and examined with results to be given.

TABLE V.—CONDENSED TABULATED PROTOCOLS OF ANIMALS AFTER ANTERIOR-LOBE FEEDING OF SINGLE MALE I, AS COMPARED WITH THE CONTROL MALE OF PAIR II.

(Protocols given up to the time of removal of the right testis in each animal, at the age of 65 days.)

Date.	Single Male I. Anterior-lobe feeding for 40 days.	Male of Pair II. Control. No glandular administration.
Mar. 8.	Weight, 23.6 gms.	Weight, 23.4 gms.
Mar. 12.	Weight, 25.9 gms. Testes not descended. Animal has been gaining slightly in weight.	Weight, 22.3 gms. Testes not descended.
Mar. 15.	Testes just descended.	Testes not descended.
Mar. 23.	Weight, 38.6 gms. Testes completely descended. Rat very vigorous. Genitalia larger than those of control.	Weight, 35 gms. Testes not completely descended. Genitalia smaller than those of Male I.
Mar. 30.	Weight, 61.8 gms.	Weight, 46 gms.
Apr. 6.	Weight, 82 gms. Genitalia definitely larger than those of control.	Weight, 70.1 gms. External genitalia definitely smaller than those of Male I.
Apr. 13.	Weight, 85.5 gms. Rat larger in general than control. More vigorous. Testes larger and firmer on palpation. Fur thicker and harsher.	Weight, 80.2 gms. Genitalia smaller than those of Male I. Fur soft and delicate.
Apr. 18.	Age of animal, 65 days. Larger and more vigorous than control. Right testis removed surgically.	Age of animal, 65 days. Lightly anesthetized with ether and right testis similarly removed.

GROSS AND MICROSCOPIC EXAMINATION OF THE TESTES REMOVED

Weight of right testis, 0.980 gm. after fixation in formalin. Testis larger and firmer on palpation and more vascular than that of control. <i>Spermatogenic tubules</i> show beginning spermatogenesis and are lined with many cell-layers, showing very active karyokinesis. <i>Spermatozoa</i> are abundant in many of the tubules. Numerous <i>spermatids</i> .	Weight of right testis, 0.570 gm. after fixation in formalin. Testis smaller, less vascular and less firm than that of Male I.
<i>Spermatogenic tubules</i> lined with one or two cell-layers. <i>Spermatogenic cells</i> abundant. <i>Spermatozoa</i> few. <i>Spermatids</i> few.	<i>Spermatogenic tubules</i> lined with one or two cell-layers. <i>Spermatogenic cells</i> few. <i>Spermatozoa</i> few. <i>Spermatids</i> few.
<i>Interstitial cells</i> in fair number. No great difference in number from those in testes of control.	<i>Interstitial cells</i> in fair number. No great difference in number from those in testes of control.
<i>Epithelium</i> : Tubules larger and lining columnar cells taller and more protoplasmic. Tubules contain <i>spermatozoa</i> .	<i>Epithelium</i> : Tubules smaller and lining columnar cells shorter and less protoplasmic. Tubules contain few cells or <i>spermatozoa</i> .

The results obtained from the feeding of anterior-lobe extract to Single Male I, beginning when the animal was 25 days old and continuing over a period of 40 days, compared with conditions in the control male of Pair II, may be summarized as follows. At the beginning of the experiment the animals were of practically the same weight. Anterior-lobe feeding had a definitely stimulating effect upon the growth of the fed animal, apparent not only in the rapid gain in weight but also in the increase in growth and in its more vigorous appearance. There was also an earlier descent of the testis and a tendency for the fur to become harsher and thicker than that of the control. In the gross, furthermore, the gland appeared larger and more vascular than the testis of the control. The gross difference in size of the testes of these two animals is well represented by the photographs (Fig. 7A), which show the actual dimensions. The body of the testis of the animal receiving anterior-lobe extract measures 3 mm. longer than the control. Its weight not only absolutely, but also in proportion to the body-weight, was very nearly twice as great as in the control, namely, 0.980 gm. as compared with 0.570 gm. Histologically, it has the appearance of maturity (Fig. 7) at the age of 65 days, or 2½ months, after 40 days of anterior-lobe feeding. The control at this period (Fig. 8) shows a relatively very much underdeveloped and immature testis. It thus becomes evident that the administration of anterior-lobe extract shortened the period of complete sexual development by one month, or about one-third—a very considerable proportion of the brief period of sexual development in the rat. The remarkable maturity (Fig. 7) of the testis of the animal receiving anterior-lobe feeding at or before the age of 65 days—well before the normal time—is evidenced histologically by a very active karyokinesis; the tubules are lined with the typical cell-rows (spermatogonia, spermatids, spermatocytes, spermatozoa) in regular order, and spermatozoa are abundantly present. In fact the testis gives evidence of being more active than the testis of a normal adult rat of from three to four months of age. The testis of the control (Fig. 8) is still immature; there is practically no karyokinesis and no spermatogenesis, the tubules being lined merely with one or two rows of undifferentiated cells. The interstitial cells do not seem to increase in number proportionately to the increase in spermatogenic cells and spermatozoa.

A COMPARISON OF THE RELATIVE STIMULATING EFFECTS OF POSTERIOR- AND ANTERIOR-LOBE (PITUITARY) FEEDING UPON GENERAL AND TESTICULAR DEVELOPMENT.

With the positive demonstration, as shown in the preceding table, of the definite stimulating action of anterior-lobe extract upon the development of the sex glands, interest was aroused in the comparative effect of posterior-lobe feeding. To test this point two male rats in Lotter III were used—the male of Pair I and the single male. It so happened that the single male, to whom anterior-lobe extract was administered, suffered from a complication (intestinal distention) following surgery.

cal removal of the right testis in another study, and for this reason had to be sacrificed at the age of $3\frac{1}{2}$ months, after $2\frac{1}{2}$ months of anterior-lobe administration. The male of Pair I continued to receive posterior-lobe extract over a period of $7\frac{1}{2}$ months, until he was sacrificed at the age of $8\frac{1}{2}$ months. An interesting comparison of the results in the two animals was then made, as shown in the accompanying table. The growth of the animal fed with anterior lobe, not only in general but also as regarded the sex glands, was considerably in excess of that of the male of Pair I, to which posterior-lobe extract was administered; and in spite of the great difference in the ages of the animals at autopsy ($3\frac{1}{2}$ months as compared with $8\frac{1}{2}$ months), the development of the sex glands was farther advanced in the animal aged $3\frac{1}{2}$ months, after anterior-lobe feeding, than in the animal receiving posterior lobe, at the age of $8\frac{1}{2}$ months. This would appear to be rather striking evidence that posterior-lobe extract does not bring about a stimulus to development of the sex glands in any way comparable to that exerted by anterior-lobe extract.

Male, Pair I.—Posterior-lobe extract, 0.1 gm. daily for 14 days, beginning March 9, when the animal was 25 days old; then 0.05 gm. daily for 7 months, or until the animal was sacrificed, October 25, at the age of 8 months and 16 days.

Single Male.—Anterior-lobe extract, 0.1 gm. daily for 14 days, beginning March 9, when the animal was 25 days old; then 0.05 gm. for 2 months, or until sacrificed June 1, at the age of 3 months and 16 days.

TABLE VI.—A COMPARISON IN TWO MALE RATS OF THE INFLUENCE OF POSTERIOR-LOBE FEEDING OVER A LONG PERIOD ($7\frac{1}{2}$ MONTHS) AND ANTERIOR-LOBE FEEDING OVER A SHORT PERIOD ($2\frac{1}{2}$ MONTHS).

LITTER III.		
Date.	Male, Pair I. Posterior-lobe feeding $7\frac{1}{2}$ months. Age at autopsy, $8\frac{1}{2}$ months.	Single Male. Anterior-lobe feeding $2\frac{1}{2}$ months. Age at autopsy, $3\frac{1}{2}$ months.
Mar. 8.	Weight, 23.7 gms.	Weight, 23.6 gms.
Mar. 9.	Feeding of posterior-lobe extract begun, at first in 0.1 gm. doses for 14 days, then in 0.05 gm. doses for $7\frac{1}{2}$ months, or until the animal was sacrificed.	Feeding of anterior-lobe extract begun, at first in 0.1 gm. doses for 14 days, then in 0.05 gm. doses for 2 months, or until the animal was sacrificed.
May 17.	Weight, 124.5 gms. Rat not as large and vigorous as anterior-lobe-fed animal. Fur thinner and more delicate. External genitalia smaller.	Weight, 146.9 gms. Rat has grown more rapidly and has gained in weight much faster than male, Pair I, which received posterior-lobe extract. Fur is harsher and thicker. Animal is more vigorous in general. External genitalia, both on inspection and on palpation, are definitely larger than those of animal fed posterior lobe.
June 1.	Animal growing. Testes moderately large. Tendency to diarrhoea from beginning of posterior-lobe feeding.	Animal sacrificed because of complication following surgical removal of right testis. Age $3\frac{1}{2}$ months. <i>Right Testis:</i> Weight, 1.720 gms. Large and normal in appearance. <i>Seminal vesicles</i> large, filled, and tense. <i>Feces</i> formed at all times.
Oct. 25.	Animal sacrificed. Age $8\frac{1}{2}$ months. Weight of right testis and epididymis, 2.28 gms. Weight of left testis and epididymis, 2.240 gms. Weight of seminal vesicles and vasa, 2.420 gms. Testis large and of normal appearance. Fair amount of secretion in seminal vesicles.	

HISTOLOGICAL COMPARISON OF TESTIS OF MALE, PAIR I, AT THE AGE OF $8\frac{1}{2}$ MONTHS AND AFTER $7\frac{1}{2}$ MONTHS OF POSTERIOR-LOBE FEEDING, WITH TESTIS OF SINGLE MALE AT THE AGE OF $3\frac{1}{2}$ MONTHS AND AFTER $2\frac{1}{2}$ MONTHS OF ANTERIOR-LOBE FEEDING.

Left Testis: Weight, 2.240 gms. *Left Testis:* Weight, 1.720 gms. *Spermatogenesis* observed but *Spermatogenesis* active and more not active. Tubules present a more abnormal appearance than in testis of anterior-lobe-fed animal, in that the lining cell layers are fewer and the lumina contain many immature, elongated spermatozoa and relatively few mature ones, although the animal was $8\frac{1}{2}$ months old.

Epididymis: The lumina here are somewhat larger than in the epididymis of the single male. The lining columnar cells are not as tall. There are many spermatozoa in the tubules, and few other cells.

Interstitial cells are few and small.

Vascularity is less than in single male (anterior-lobe feeding).

Prostatic Gland: The acini are larger and fewer in number; there is very little infolding of the epithelium, which is composed of low cubical cells. The lumina of the acini are distended with a homogeneous pink-staining secretion. Very few young newly formed acini (cf. Fig. 8).

Seminal Vesicle: Smaller, less distended; epithelial lining lower and less branching into the lumen.

Vas Deferens: Smaller, not distended with secretion; contains no spermatozoa. Epithelium less tall and less ciliated. Muscle coat less bulky.

Seminal Vesicle: Larger, markedly distended with secretion; epithelium slightly taller and shows much infolding.
Vas Deferens: Larger, distended with secretion containing great numbers of spermatozoa. Epithelium tall, more ciliated. Muscle coat thicker.

A comparison of the results of anterior- and posterior-lobe feeding given in Table VI shows, in brief, that anterior-lobe feeding over a period of $2\frac{1}{2}$ months has produced not only a greater bodily growth and development, but also a more rapid genital development than has followed posterior-lobe feeding for $7\frac{1}{2}$ months. Indeed it would seem, as heretofore stated, that posterior-lobe feeding has had a distinctly retarding influence upon the development of the sex glands, for otherwise it would be difficult to understand the incomplete development of the testis of the male of Pair I, at the age of $8\frac{1}{2}$ months, as compared with the testis of the single male at the age of $3\frac{1}{2}$ months. In other words, anterior-lobe feeding for $2\frac{1}{2}$ months has caused a more active and advanced spermatogenesis at the age of $3\frac{1}{2}$ months than is observed in the testis of the animal aged $8\frac{1}{2}$ months, after $7\frac{1}{2}$ months of posterior-lobe feeding. This effect of anterior-lobe feeding corresponds with the results in a previous experiment (Table V).

Posterior-lobe feeding also tends to produce intestinal peristalsis, as indicated by the persistence of an occasional slight diarrhoea.

Anterior-lobe extract does not seem to cause any marked change in the number of interstitial cells. In the epididymis, however, the tubules are lined with taller and larger cells, and there are more spermatozoa and free cells in the lumina. The vascularity of the testis and epididymis is also increased.

Thus it would appear that no matter what may be the age, even after maturity, of the animal receiving posterior-lobe



FIG. 7. Single Male I (anterior-lobe feeding).

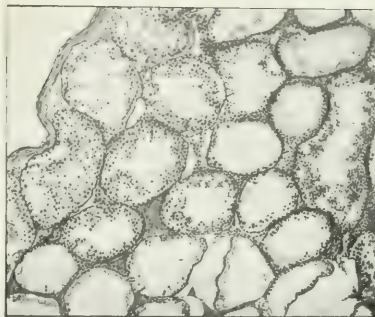


FIG. 8.—Male, Pair II (control).

Figs. 7 and 8. Sections of right testes of two young rats of the same litter, removed when the animals were 45 days or 2½ months old. Testes in gross shown in Fig. 7A.

Fig. 7. Typical appearance in section of the right testis of Single Male I, to which anterior-lobe extract was given over a period of 40 days from the time when the animal was 25 days old.

Fig. 8. Typical appearance in section of the right testis of Male, Pair II, control, receiving no gland extract.

Note in Fig. 7 the very active mature development of spermatogenesis with the production of numerous spermatozoa.

Note in Fig. 8 the immature development of the spermatogenic tubules with very little cell division and without spermatozoa. Tubules lined simply with one or two rows of primitive spermatogenic cells.

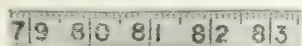


FIG. 7A.—Photographs (actual size) of the right testes of Single Male I (anterior-lobe feeding for 40 days) and Male, Pair II, control (without gland feeding). The testis represented in the lower photograph, and taken from the animal receiving the anterior-lobe extract, weighed 0.980 gm. as compared with 0.570 gm. the weight of the testis of the control represented in the upper photograph.

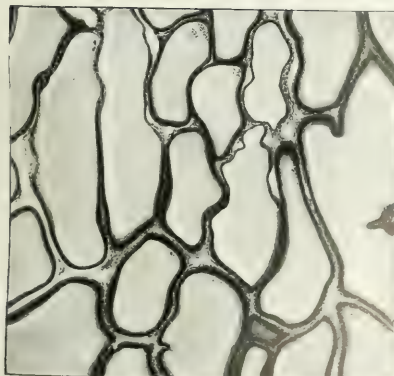


FIG. 9. Male, Pair I (posterior-lobe feeding 7½ months). Age of animal at autopsy, 8½ months. $\times 55$.

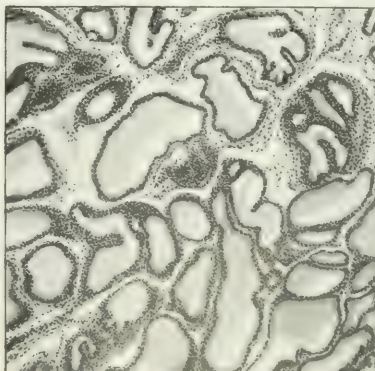


FIG. 10.—Single Male (anterior-lobe feeding 2½ months). Age of animal at autopsy, 3½ months. $\times 55$.

Fig. 9. Representative section from the prostatic gland of a rat 8½ months old, after feeding of pituitary posterior-lobe extract for 7½ months.

Fig. 10. Similar representative section from the prostatic gland of a rat 3½ months old of the same litter III, after only 2½ months of feeding of pituitary anterior-lobe extract.

Note the hyperplastic appearance of the prostatic gland (Fig. 10) in the animal who had received anterior-lobe extract, notwithstanding the fact that this animal was far younger than the male whose prostatic gland is represented in Fig. 9; an indication of the marked stimulating action of the anterior-lobe extract and the possible inhibiting action of posterior-lobe extract.

extract, the testis never reaches the stage of development and activity observed in the testis of an animal receiving anterior-lobe feeding.

In a previous experiment (page 39, Table V) and in Figs. 7 and 8 evidences are given for believing that anterior-lobe feeding has a marked stimulating action upon the development of the testis. The prostatic gland, seminal vesicle and vas deferens were not examined in this case. This stimulating action of the anterior-lobe extract was undoubtedly exerted upon the latter organs also, for in the experiment just quoted we find evidences of increased and active development on the part of the prostatic gland, seminal vesicle and vas deferens as well as the testis, as a result of a brief period (2½ months) of anterior-lobe administration, as compared with posterior-lobe administration over a period of 7½ months. To illustrate this point, representative sections from the prostatic glands of the two males under consideration were drawn, and are shown in Figs. 9 and 10. The differences are striking, and the figures with their legends are self-explanatory.

In Table VI it is stated that the testis of the male of Pair I, the animal receiving the posterior-lobe extract, shows a very inactive spermatogenesis in comparison with the testis of the single male fed with the anterior-lobe powder. As a result, as would be expected, there are very few mature spermatozoa in the former, whereas in the latter spermatozoa are very abundant. As an index of the active spermatogenesis produced by anterior-lobe feeding we have, in addition to the appearance of the testes themselves, the presence of great numbers of spermatozoa in the secretion distending the vas deferens in the former (Figs. 12 and 12A), while in the case of the animal receiving posterior-lobe powder the vas contains no spermatozoa, and no secretion, and the walls are collapsed (Fig. 11). These differences in spermatogenic activity are all the more striking when one realizes that the animal receiving the anterior-lobe feeding (Fig. 12) was only 3½ months old, while the animal receiving posterior-lobe feeding was 8½ months old when the autopsy was performed.

THE EFFECT OF PROLONGED FEEDING OF PITUITARY (ANTERIOR LOBE) EXTRACT UPON BREEDING AND PREGNANCY AND UPON THE FINAL DEVELOPMENT AND HISTOLOGICAL APPEARANCE OF THE SEX GLANDS.

In view of the definite stimulating influence of anterior-lobe feeding upon the development of the genital system in both male and female, resulting in the early maturity of testes and ovaries, it was thought of interest to observe the effect of anterior-lobe feeding on one pair of rats, using as controls a second pair of the same litter without glandular administration, in order to determine whether, with the early histological maturity, the sexual instincts were also prematurely developed, and also whether the animals were fertile at the early age at which the testes and ovaries were known to be mature. The animals were observed for a sufficient length of time to enable us to draw some fairly definite conclusions. They were kept in adjoining cages under precisely similar circumstances and under conditions as nearly quiet and undisturbed as possible.

At the beginning of the observation both the male and the female of the control pair were a trifle larger and heavier than the pair selected for the feeding of anterior lobe, and thus the odds of the experiment were placed in favor of the control animals.

Two pairs of rats of Litter I, born January 31, 1913, were used in this observation. On March 5 the weights were as follows: Male, Pair I, 32.1 gms.; male, Pair II, 33.3 gms.; female, Pair I, 27.6 gms.; female, Pair II, 29.7 gms. The lighter pair, as stated, were selected for the glandular feeding, the heavier, Pair II, being used for control. The feeding of anterior-lobe extract was begun on March 6, in daily doses of 0.1 gm., and was continued in this dosage for 16 days, after which time 0.05 gm. was given daily until November 22, when the animals were sacrificed. The feeding was thus begun when the animals were 34 days old and was continued for approximately 8½ months.

Pair I, Male and Female.—Anterior-lobe extract for a period of 8 months, beginning when the animals were 34 days old. Both were sacrificed when approximately 10 months old (accurately, 9 months and 22 days).

Pair II, Male and Female.—Used as controls. The autopsy on the male was done at the age of 10 months, and on the female at the age of 7 months and 6 days.

The condensed protocols are given in tabulated form in Table VII, to show the general effect of continued anterior-lobe feeding upon growth, weight and development, and upon the time of breeding, the rapidity of successive pregnancies and the size of the litters. In Table VIII are given the histological findings at the age of 10 months in the ovaries and testes of the pair receiving anterior-lobe feeding, as compared with the findings in the sex glands of the control pair—in the male at the age of 10 months and in the female at the age of 7 months and 6 days, at which age this animal, although adult and mature, died suddenly.

In summarizing the comparative observations on the male of Pair I (anterior-lobe feeding) and the control male of Pair II, it is seen that—in spite of the fact that at the beginning of the experiment, when the rats were weaned, the male of Pair I weighed less than the control male of Pair II (32.1 gms. as compared with 33.3 gms.)—nevertheless, the male of Pair I, receiving anterior-lobe extract, very soon overtook the control male in weight (cf. under March 30). This difference in weight gradually increased during the succeeding 7 months, until at the end of the experiment, when the animals were sacrificed, the weight of the animal receiving anterior-lobe feeding was 256.8 gms., or 26.4 gms. in excess of the weight of the control (cf. November 22 and 30). With this marked increase in weight there was a more active development of the external genitalia, and an earlier complete descent of the testes, which even on gross inspection and palpation were definitely larger than those of the control male. There was also an increased weight of the testes both absolutely and proportionately to the body weight. Thus, for example, using the right testis of each animal for comparison, the weight of the testis in the case of the male receiving anterior-lobe extract was 0.73 gm. per 100 gms. of body weight, as compared with 0.59

TABLE VII.—CONDENSED TABULATED PROTOCOLS OF TWO PAIRS OF RATS OF LITTER I, TO SHOW THE CONDITIONS AFTER PROLONGED FEEDING OF ANTERIOR-LOBE EXTRACT TO PAIR I, AS COMPARED WITH THOSE IN CONTROL PAIR II RECEIVING NO GLANDULAR EXTRACT.

(With special reference to weight, growth, development, breeding, pregnancies, and the size of the litters.)

	Pair I. Anterior lobe feeding for 8½ months, begun Mar. 5		Pair II. Control. No glandular administration.	
Date	Male. Age at autopsy, 10 months	Female. Age at autopsy, 10 months	Male. Age at autopsy, 10 months.	Female. Age at autopsy, 7 months, 1 week.
Mar. 5	Weight, 32.1 gms.	Weight, 27.6 gms.	Weight, 33.3 gms.	Weight, 29.7 gms.
Mar. 12	Weight, 38.7 gms. Testes descended at all times	Weight, 29.9 gms. Smaller than mate.	Weight, 37.9 gms. Testes at times descended, at other times disappear into abdomen. Vigorous-looking animal	Weight, 32.2 gms. Nothing of special note.
Mar. 18	Weight, 41.0 gms. Testes descended. Hair delicate. Animal active and playful.	Weight, 29.7 gms. Animal in good condition.	Weight, 43.3 gms. Testes fairly large, and descended at all times.	Weight, 32.4 gms.
Mar. 23	Weight, 58.9 gms. External genitalia quite large. Slight tendency to diarrhoea	Weight, 43.5 gms. Nipples barely perceptible. Tendency to diarrhoea	Weight, 61.8 gms. External genitalia about as in male of Pair I. No tendency to loose bowel movements.	Weight, 49.3 gms. Nipples as in female of Pair I. No looseness of bowel movements.
Mar. 30	Weight, 68.8 gms. Animal has overtaken control male in weight.	Weight, 51.9 gms. Nipples quite distinctly visible and well marked.	Weight, 66.1 gms. External genitalia about as in male of Pair I.	Weight, 52.7 gms. Nipples prominent, though possibly less so than in female of Pair I.
Apr. 6	Weight, 90.6 gms. Rat more vigorous than control. External genitalia larger than those of control	Weight, 69.9 gms. Hair thicker and harsher than that of control.	Weight, 84.8 gms. Animal not as vigorous as male of Pair I.	Weight, 62.6 gms. Hair softer, thinner and more delicate than that of female of Pair I.
Apr. 20	Weight, 108.2 gms.	Weight, 79.2 gms.	Weight, 89 gms.	Weight, 68.6 gms.
May 17	Weight, 144 gms. Animal larger in general than control. Testes definitely larger.	Weight, 113.1 gms. Nipples more prominent, abdomen fuller than in control.	Weight, 122.9 gms. Genitalia smaller than those of male of Pair I.	Weight, 95.3 gms. Nipples very small; just visible
June 1	Weight, 167.4 gms. Testes larger than those of control male.	Weight, 146.4 gms. Animal pregnant. Has gained 21 gms. in weight in one week. As large as male of this pair. Nipples large. Vagina larger than that of control	Weight, 139.2 gms. Testes noticeably smaller than those of male of Pair I	Weight, 122.1 gms. Smaller than female of Pair I. Nipples very much smaller; just visible. Fur softer. Vagina smaller.
Pregnancy I.			No signs of pregnancy.	
June 4	Female of this pair gave birth on this date to a litter of six, apparently at full term. No abnormalities noted in the young, nor in the mechanism of parturition. Three were killed by the parent animal; two died of exposure, and the remaining one died on the following day. The average weight of the young was 3.9 gms. This first litter, then, was born when the parents were 124 days, or 4½ months, old.			
June 6	Male replaced in cage with female. Weight, 114 gms. Animal appears well and active.			
June 22	Weight, 182.8 gms. Animal considerably larger than control male. External genitalia still definitely larger. Hair coarser.	Weight, 124.8 gms. Nipples have become smaller, but are still definitely larger than those of control female	Weight, 150 gms. Genitalia smaller than those of male of Pair I. Hair softer and finer.	Weight, 130.6 gms. Nipples becoming slightly larger, but are definitely smaller than those of female of Pair I.
July 27	Weight, 198.9 gms. More vigorous than control. Testes considerably larger.	Weight, 140.6 gms. Nipples still definitely larger than those of control female.	Weight, 161.7 gms. Rat smaller than male of Pair I. Testes smaller.	Weight, 143.8 gms. Nipples still very small—much smaller than those of female of Pair I.
Aug. 30	Weight, 225.5 gms.	Weight, 184.6 gms. Animal pregnant the second time. Abdomen bulging in flanks.		
Sept. 1	Pregnancy II.		Weight, 189.7 gms.	Weight, 172.3 gms.
Sept. 4	Female of this pair gave birth on this date to a second litter of three. The young are normal and healthy looking. Mother in good condition. Young are designated hereafter as Rat A, Rat B, and Rat C.			
Sept. 6	Weight, 235.5 gms.	Weight, 153.9 gms.	Weight, 191.4 gms.	Weight, 155.1 gms. Animal found dead in cage on this date. Had recently lost weight. Seemed in good condition on previous day.
			Autopsy.	
			Autopsy done on same day. Very little subcutaneous fat. Some fat in omentum and mesentery. Combined weight of both ovaries, 0.145 gm. Small, reddish, hemorrhagic-looking nodules, resembling corpora lutea, in each ovary. Cornua of uterus have an edematous appearance. Death due to pneumonia.	
Sept. 28	Weight, 236.6 gms.	Weight, 160.4 gms.	Weight, 207.2 gms.	
Oct. 5	The young of the second litter, Rat A, Rat B, and Rat C, were weaned on this date. The feeding of anterior-lobe extract was begun to Rat A and Rat C, which were paired. Rat B was given ovarian extract. After further protocols of these animals see table following.			
Oct. 12	Weight, 254.9 gms.	Weight, 180.6 gms.	Weight, 222.6 gms.	
Nov. 22		Nov. 22	Nov. 30	
Weight, 256.8 gms. Animal sacrificed.		Weight, 182.6 gms. Animal sacrificed.	Weight, 230.4 gms. Animal sacrificed.	
Autopsy.		Autopsy.	Autopsy.	
Testes noticeably larger than those of control male, and more vascular. Tubules plainly visible in the gross.		Weight of ovaries, uterus and upper vagina, 0.780 gms.	Testes not especially large or vascular. Weight of right testes, 1.370 gms. Weight of left testes, 1.100 gms. Weight of seminal vesicles, prostate and bladder, 2.870 gms. Moderate amount of fat in retro-peritoneal tissues; very little in omentum. Hair not particularly coarse.	
Weight of right testis, 1.89 gms. Weight of left testis, 1.90 gms. Weight of seminal vesicles, prostate and bladder, 3.66 gms.				



FIG. 11.



FIG. 12.

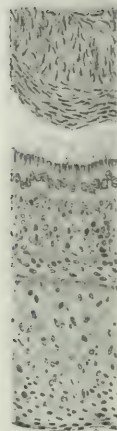


FIG. 12A.

FIG. 11.—Vas deferens of Male, Pair I (posterior-lobe feeding for 7½ months). $\times 41$.

FIG. 12.—Vas deferens of Single Male I (anterior-lobe feeding for 2½ months). $\times 41$.

FIG. 12A.—High power drawing of area (a) in Fig. 12, showing numerous spermatozoa in the lumen of the vas which is lined with tall ciliated columnar cells. $\times 170$.

Note in Fig. 12 the vas deferens distended with secretion containing large numbers of spermatozoa, as compared with the vas in Fig. 11 from which secretion and spermatozoa are absent.



FIG. 13.—Left testes, seminal vesicles and prostatic glands of two males of the same litter (*cf.* Tables XI, XII and XIII), to one of which corpus-luteum extract was fed over a period of 6 months, the other being used as the control. Note the smaller size of the sex glands in the ovarian-fed male, to the left in the figure. The weight of testis of the ovarian-fed animal was 1.93 gms., as compared with 2.30 gms. in the control; seminal vesicles and prostatic gland, 1.7 gms., as compared with 1.8 gms. in the control.

Note difference in the size of the seminal vesicles (*s. v.*) and the prostatic lobes (*p. l.*) in the two cases.

gm. per 100 gms. of body weight of the control male. The fat of the fed animal was also coarser and thicker.

In the case of the female rats similarly observed, the results are practically analogous. The weight of the female of Pair I was less at the beginning of the experiment than that of the control, being 27.6 gms., as compared with 29.7 gms. Very soon, however, the female of Pair I, receiving anterior-lobe extract, overtook the control female in weight, on April 6 weighing 69.9 gms., as compared with 62.6 gms. This over-weight increased and was maintained during the succeeding five months, except immediately following the pregnancies; and on October 12, when the animal had recovered from her second pregnancy, she weighed 180.6 gms., as compared with 155.1 gms., the best weight of the control-female, on September 6. With this increase in the weight of the female receiving anterior lobe there was also a more rapid development gener-

normal and healthy, did not breed at all. Granting naturally that a single observation of this kind is in no way conclusive, it would nevertheless seem to indicate that, although under the somewhat unfavorable laboratory conditions the control animals failed to breed at all, the feeding of anterior-lobe extract to Pair I acted as a stimulant to breeding and offset the possible inhibiting influences of the laboratory environment. In regard to the size of the litters no definite comments can be made. After the first pregnancy there were six young, a fairly large litter. The second litter, however, was a small one, consisting of only three young.

In addition to noting the effect of prolonged feeding of anterior-lobe extract upon growth, development and breeding in this experiment, it was also possible to observe whether the early signs of activity of the sex glands were still visible after 8½ months of glandular feeding; whether the normal control

TABLE VIII.—SHOWING THE LATE EFFECT UPON THE WEIGHT AND HISTOLOGICAL APPEARANCE OF THE SEX GLANDS IN A PAIR OF RATS AFTER PROLONGED FEEDING OF PITUITARY ANTERIOR-LOBE EXTRACT AS COMPARED WITH THE CONDITIONS IN ANOTHER PAIR RECEIVING NO GLANDULAR EXTRACT.

LITTER I.

Pair I, Male. Anterior-lobe feeding 8½ months. Weight, 256.8 gms.	Pair II, Male, Control. No glandular administration. Weight, 230.4 gms.	Pair I, Female. Anterior-lobe feeding 8½ months. Weight, 182.6 gms.	Pair II, Female, Control. No glandular administration. Weight, 172.3 gms.
Weight of left testis, 1.90 gms. Weight of right testis, 1.89 gms. <i>Spermatogenesis</i> active. Tubules contain a fair number of spermatozoa and are lined with several rows of cells in typical order.	Weight of left testis, 1.46 gms. Weight of right testis, 1.570 gms. <i>Spermatogenesis</i> less active than in male of Pair I. Tubules contain fewer spermatozoa and are lined with fewer cell layers.	Weight of ovaries, uterus and upper vagina, 0.780 gms. Ovary larger than that of the female of Pair II, and contains very few primordial, several medium-developed and a few large follicles. There are several vacuolated cellular corpora lutea, with beginning formation of corpora fibrosa.	Weight of ovaries, uterus and upper vagina, 0.145 gms. Ovary smaller than in the female of Pair I, and contains more primitive follicles, more developing and more mature follicles. Corpora lutea fewer in number, larger and less fibrous and organized, i. e., younger. Corpora hemorrhagic seen in the gross specimen.
<i>Epididymis</i> contains a great many spermatozoa. The lining cells contain a large amount of lipoidal substance; there is vacuolation about the nuclei; the cells are more ciliated.	<i>Epididymis</i> contains few spermatozoa—much less numerous than in the male of Pair I. Lumina of tubules smaller, less tall, contain less lipoidal substance and show less vacuolation about the nuclei.	<i>Interstitial tissue</i> rich in cells.	<i>Interstitial tissue</i> abundant and cellular.
<i>Interstitial cells</i> present in fair number; more numerous than in the control male.	<i>Interstitial cells</i> are very few in number; they appear definitely fewer than in the male of Pair I.	<i>Vasculature</i> , as seen at hilus, greater than in the female of Pair II.	<i>Vasculature</i> , as seen at hilus, less than in the female of Pair I.
<i>Testis</i> larger and more vascular on gross inspection than that of the male of Pair II.	<i>Testis</i> smaller and less vascular on gross inspection than that of the male of Pair I.	<i>Fimbriated</i> end of tube much branched, and lined with tall, ciliated columnar cells.	<i>Fimbriated</i> end of tube branched, less active-looking.
<i>Seminal Vesicles and Prostate.</i> Weight, 3.06 gms. No special difference from male of Pair II, except as to size and the larger number of spermatozoa.	<i>Seminal Vesicles and Prostate.</i> Weight, 2.820 gms. Definitely smaller than in the male of Pair I; contain few free cells and spermatozoa.	<i>Fallopian tube</i> lined with tall cells, partly ciliated; mucous membrane much folded; muscle coat thick.	<i>Fallopian tube</i> smaller; lining cells less tall; lumen larger; less folded mucous membrane, muscle coat thicker.
		<i>Cornu of uterus</i> lined with thick, much folded mucous membrane, containing a few glands; lumen smaller than in female of Pair II; vasculature greater. Muscle coat well developed.	<i>Cornu of uterus</i> lined with thinner, less folded, less vascular mucous membrane, containing no glands. Muscle coat less well developed.

ally; the nipples became larger and the hair coarser and thicker.

In regard to breeding, pregnancy and parturition, it is interesting to note that Pair I, receiving anterior-lobe extract, bred at the early age of 3½ months and that the female gave birth to a litter of six young when she was 4 months and 1 week old (cf. June 1)—a fact which demonstrates that the instincts are early awakened and that the female can be impregnated at this comparatively early age as a result of the premature histological maturity of the testis and ovary produced by the feeding of anterior-lobe extract. This latter effect was also shown in an earlier experiment (Tables V, VI and VII).

There was nothing abnormal noticed about either pregnancy. The second pregnancy and delivery of three young occurred after an interval of three months—which may be considered rather rapidly succeeding pregnancy under the somewhat abnormal breeding conditions of a laboratory. There were then, two pregnancies in the pair receiving anterior-lobe extract, by the time the animals were 10 months old. During this period the control pair, although they appeared normal, did not

animals in due time reached the stage of development acquired much earlier by the fed animals, and whether the early over-development of the sex glands of the fed animals, as compared with the controls, was maintained throughout the subsequent adult life of the animals.

Table VIII gives the weights of and histological findings in the sex glands of the male and female rats of Pair I, Litter I, fed with anterior-lobe extract for 8½ months, as compared with the sex glands of the control male and female of Pair II. The control female, though younger at the time of autopsy than the female receiving anterior lobe, was nevertheless mature enough to serve for the purpose of comparison as a normal adult control rat.

The results in the case of the two males will be summarized first. Both animals were approximately 10 months old when they were sacrificed—fully matured adult rats. It will be seen that the sex glands of the animal receiving anterior-lobe extract over a period of 8½ months still continued to show a greater and more active development than those of the control. This is indicated by the following findings: The weight of the

testis is greater, both absolutely and in relation to the body-weight; spermatogenesis is more active; the epididymis contains many more spermatozoa and is made up of tubules with larger lumina and taller lining cells, containing more lipoidal substance; the interstitial cells of the testis are more numerous; the seminal vesicles and prostatic gland are larger and heavier; the vas deferens is larger and more distended, and contains many more spermatozoa; and the vascularity of the testis is greater in general. These results are at variance with those of Behrenroth, who states that in a short time the control animal reaches the stage of development of the fed animal, thus suggesting that the effect of pituitary administration (in his experiments by subcutaneous injections) lasts only for a time in the early life of the animal, and that there are no permanent or late changes.

In comparing the results in the females we find that the differences observed in the weight and appearance of the sex glands are comparable to those in the sex glands of the males. The control female of Pair II died of acute pneumonia at the age of 7 months and 1 week, but this discrepancy in age, though unfortunate for a precise comparison, nevertheless does not alter the value of the observation, for after the age of 7 months a difference of 2 months in age would make practically no appreciable alteration in the histological appearances of the ovaries and uteri. Furthermore, the differences observed in these two animals are far in excess of any change that could be attributed to the difference in their ages. Thus we find that the ovary of the fed animal is larger in the gross than that of the control. (A record of the weight of the ovaries alone was unfortunately lost.) Also the ovary of this animal contains a number of corpora lutea with beginning formation of corpora fibrosa, several large and medium-sized Graafian, and a few primordial, follicles. The ovary of the control contains a greater number of primordial follicles, more developing and mature Graafian follicles and few corpora lutea, which in this animal are younger, less fibrous and less organized. In the gross specimen corpora hæmorrhagica were also observed. These findings would seem to indicate that the ovary of the female receiving anterior-lobe feeding is an older, a more senile ovary, so to speak, which has run its course and has undergone a far more extensive ovulation, as indicated by the few primordial follicles and the presence of corpora fibrosa. Furthermore, the ovary of the fed animal shows a rich amount of interstitial tissue and a greater vascularity than that of the control; the Fallopian tube has a more highly branched fimbriated extremity, the lining cells of the tube are taller and more uniformly ciliated, and the muscle coat is thicker; the uterus is lined with a thicker endometrium, which is more vascular and more folded, contains glands which are absent in the control and has a heavier musculature.

We have, then, evidence that pituitary anterior-lobe extract exerts its stimulating influence upon both the male and the female sex glands, not only in early life but also well into the adult period, and that this influence is not specific for any single part, but affects the whole of the sexual system.

THE INFLUENCE OF ANTERIOR-LOBE FEEDING CARRIED THROUGH THE PARENTS INTO THE SECOND GENERATION.

We have seen that the feeding of anterior-lobe extract to young rats causes an early maturity of the testes and ovaries, and we might therefore expect early breeding and pregnancies with possibly larger litters, since ovulation is markedly stimulated. It also seems reasonable to suppose that the younger the animal at the beginning of the glandular administration, and the longer the feeding is continued, the more marked will be the stimulating action exerted. The possibility was thus suggested of subjecting an animal to anterior-lobe stimulation during intra-uterine life and during the period of lactation by administering the extract to the mother, and at the end of the period of lactation by giving the glandular extract by mouth as in the case of the parents. A single experiment, which yielded several suggestive findings, may be here reported.

To the parent pair of Litter I (*cf.* Table VII) anterior-lobe extract had been given from the time when the animals were 34 days old, and was continued during the two pregnancies—in fact until the animals were sacrificed. As a result of the second pregnancy a litter of three rats was born; these are designated as Rat A (female), Rat B (male) and Rat C (male). The young having been weaned at the age of 31 days, a daily dose of 0.05 gm. of anterior lobe in pill form was given to Rat A and Rat C, which were paired. To the remaining male, Rat B, ovarian extract (*corpus luteum*) was given daily in the same dosage. In this way Rat A and Rat C were subjected throughout their intra-uterine as well as extra-uterine life to anterior-lobe stimulation. It was believed that in this way an even greater body growth and an earlier and more active sexual development could be produced than in the experiments heretofore reported. In the case of Rat B, the remaining male, ovarian extract, for the sake of comparison, was substituted for the anterior-lobe feeding.

Although the facts as brought out in this single observation are in no way conclusive, they are nevertheless very suggestive and for this reason are given here. The more rapid growth and increase in weight of the rat of the second generation is well illustrated in Rat C as compared with his male parent. At corresponding ages it is found that Rat C was considerably heavier than his male parent. Thus, soon after weaning, when 34 days old, the parent male weighed 32.1 gms., whereas Rat C, when only 31 days old, weighed 51.7 gms. Again, at the age of 80 days the parent male weighed 108.2 gms., as compared with 126.6 gms., the weight of the young Rat C at the same age. In the case of the females the difference in weight at the age of 80 days is even more striking, the parent female weighing 79.2 gms. as compared with 117.1 gms., the weight of the female offspring.

In regard to the time of breeding and the first pregnancy we find that Rat A and Rat C of the second generation bred at the age of 74 days, as compared with 104 days, or $3\frac{1}{2}$ months, in the case of the parent pair. In the case of the parent pair the first litter was born after 125 days, or $4\frac{1}{2}$ months, as compared with 95 days, or $3\frac{1}{2}$ months for the young pair. Thus

we see that breeding and pregnancy occurred one month earlier in the pair of the second generation—a period more than one-third of the normal time of adolescence of the rat—considerably earlier than the average normal breeding-time. We see, too, that the litter born to the pair of the second generation numbers eight as compared with six in the litter of the parent pair. The average weight of the young, however, is greater in the litter of the parents, the average being 3.9 gms. as compared with 3.56 gms., the average weight of the young in the litter of the second generation. So far, then, as the results of

A comparison may also be made between the two males, Rat C and Rat B, the former receiving anterior-lobe stimulation throughout, and this effect in the latter being interrupted by the substitution of ovarian feeding when the animal was weaned. The feeding of anterior-lobe and ovarian extracts was continued during the succeeding 6 months. Both animals were sacrificed on March 30, 1914, at the age of 7 months. At the beginning of the experiment the slight advantage in growth and development was in favor of Rat B, which received the ovarian extract (*cf.* difference in weight September 22).

TABLE IX.—CONDENSED TABULATED PROTOCOLS SHOWING THE EFFECT OF ANTERIOR-LOBE FEEDING IN PARENT PAIR CARRIED THROUGH THE YOUNG OF THE SECOND GENERATION.

LITTER I, PAIR I (PARENTS). ANTERIOR-LOBE FEEDING.

A litter of three rats born Sept. 4. Rat A (female), Rat B (male), Rat C (male). Rat A paired with Rat C.			
Date.	Rat A (female). Anterior-lobe feeding, begun Oct. 5.	Rat B (male). Anterior-lobe feeding, begun Oct. 5.	Rat C (male). Ovarian feeding, begun Oct. 5.
Sept. 22.	Weight, 23.8 gms.	Weight, 26.8 gms.	Weight, 27.9 gms.
Sept. 26.	Weight, 26.2 gms.	Weight, 29.3 gms.	Weight, 30.5 gms.
Sept. 28.	Weight, 34.2 gms.	Weight, 39.1 gms.	Weight, 43.9 gms.
Oct. 5.	Weight, 47.8 gms. Weaned on this date and paired with Rat C (male). Anterior-lobe feeding begun. Vaginal septum not yet perforated.	Weight, 51.7 gms. Weaned and paired with Rat A (female). Anterior-lobe feeding begun. Testes descended and fairly large.	Weight, 57.4 gms. Weaned on this date. Ovarian feeding begun, for comparison with Rat C (anterior-lobe feeding). Testes descended.
Oct. 12.	Weight, 57.2 gms. Vaginal septum not yet ruptured.	Weight, 63.4 gms. Animal smaller than Rat B (ovarian f.d.). Testes large—possibly slightly larger than testes of Rat B.	Weight, 78.1 gms. Larger generally than Rat C, receiving anterior-lobe.
Oct. 19.	Weight, 67.4 gms. Vaginal septum unruptured.	Weight, 73.9 gms. Testes possibly slightly larger than those of Rat B.	Weight, 89.6 gms.
Oct. 26.	Weight, 92.8 gms. Hymen ruptured. Free entrance into vagina.	Weight, 105 gms.	Weight, 123.5 gms.
Nov. 22.	Weight, 117.1 gms. Nipples still quite small.	Weight, 126.6 gms. Animal smaller than Rat B (ovarian-fed).	Weight, 165 gms. Testes quite large.
Dec. 1.	Weight, 136.8 gms. Domelet regressed. Rapid gain in weight. Abdomen full; blood-stained secretion in vagina. Nipples rapidly increasing in size. (Pregnancy in less than three months.)	Weight, 136.3 gms. Although animal is smaller generally than Rat B, the testes are as large, if not larger, than those of the ovarian-fed animal. Rat removed from female to-day.	Weight, 173 gms. Animal has grown larger and has become fat more rapidly than male Rat C (anterior-lobe). Fur seems heavier and coarser (similar facts observed in the case of ovarian-fed male of Litter I— <i>cf.</i> Table XI.)
Dec. 8.	Rat A, weight, 160.5 gms. Gave birth to-day to a litter of eight young. Three died soon after birth, and one was killed by the parent rat. One of the dead young still in its membranes with cord and placenta attached. The dead young present no abnormalities, but are smaller than the four living. Mother neglected the young, as in the case of the first pregnancy of the parents, Litter I, Pair I. Fair amount of bleeding during parturition. Average weight of three of the dead young, 3.56 gms. Weight of mother after birth of litter, 125.1 gms.	March 30, 1914. Animal kept until March 30, 1914, when it was sacrificed and autopsied.	March 30, 1914. Animal kept until March 30, when it was sacrificed and autopsied.
Dec. 19.	Weight 122 gms. Animal anesthetized on this date for X-ray photograph, and died under the anesthetic, thus preventing further comparison. The animal was still remarkably small, considering the recent pregnancy. Vagina and uterus unusually small, though quite vascular, probably from pregnancy. Ovaries quite large, and contain corpora hemorrhagica and lutea.	Weight 181 gms. External genitalia larger on palpation than those of Rat B. Weight of right testis, 1.95 gms. Weight of left testis, 2.050 gms. Weight of seminal vesicles, prostate and vas, 1.5 gms. Very little fat in general.	Weight 161.6 gms. External genitalia smaller on palpation than those of Rat C. Weight of right testis, 1.620 gms. Weight of left testis, 1.500 gms. Weight of seminal vesicles, prostate and vas, 0.760 gm. Very little fat in general.

this experiment go, they suggest that the feeding of pituitary anterior lobe to parent rats exerts an influence upon the offspring in intra-uterine life and during lactation, and that when carried further in the life of the animal, it has a markedly stimulating effect upon growth, weight and development, and causes an earlier breeding and an increased number of offspring. The results are sufficiently suggestive to encourage further experiments along this line. Whether one could eventually produce a strain of larger rats with a more active sexual life, and, on the other hand, whether the result would be overstimulation and eventual deterioration of the strain, remain interesting questions deserving further study.

There was an early increase in the weight of the ovarian-fed male over the weight of the male receiving anterior lobe, although at the end of the experiment the reverse result was very marked. Later on in the progress of the feeding, the external genitalia of the animal receiving anterior lobe were larger on gross inspection and palpation than those of the ovarian-fed animal. Furthermore, at autopsy there was found to be a very definite difference in the weight, both absolutely and in relation to body-weight, and weight of the testes, seminal vesicles, prostatic glands and vas deferens, in favor of the animal receiving anterior lobe (*cf.* under March 30). The total weight of the entire genital system in Rat C can-

terior-lobe feeding) is 5.50 gms. as compared with 3.88 gms., the weight of Rat B (ovarian feeding). Calculating upon a basis proportionate to body-weight we find that the weight of the genital system of the rat receiving anterior lobe is 3.038 gms. per 100 gms. of body-weight, as compared with 2.10 gms. per 100 gms. of body-weight in the ovarian-fed male. Here we again have a definite example of the continued stimulating action of prolonged anterior-lobe administration upon the development of the genital system.

In Table X a comparison is made of the histological appearances of the sex glands of these two males.

TABLE X.—SHOWING THE COMPARATIVE HISTOLOGICAL APPEARANCE OF THE TESTIS IN RAT C AND RAT B.

(Continued from Table IX.)

Rat C (male). Anterior-lobe feeding began when the animal was 31 days old and continued for approximately 6 months.

Right Testis: Spermatogenesis very active. Large numbers of spermatozoa are seen in the tubules, which contain a considerable amount of secretion and many free cells.

Interstitial cells are present in moderate numbers.

Epididymis: The tubules are rather large, moderately distended with secretion containing large numbers of spermatozoa. They are lined with a low columnar epithelium composed of cells having a kind of ciliated border.

Prostate Gland and Seminal Vesicle: More proliferation of the epithelium evident in the indentations and infolding of the lining cells. More secretion in the lumen. Spermatozoa are present in considerable numbers in the seminal vesicle.

Vas Deferens: The lining cells have a denser protoplasm and are more abundantly supplied with cilia. Muscle coat somewhat heavier.

Rat B (male). Ovarian feeding began when the animal was 31 days old and continued for approximately 6 months.

Right Testis: Spermatogenesis much less active. There are fewer free cells and a strikingly smaller number of spermatozoa in the tubules, which are lined with spermatozoa in fewer numbers and in less compact arrangement.

Interstitial cells are less numerous and smaller.

Epididymis: Tubules smaller and less distended with a secretion that contains relatively few spermatozoa. The lining cells are of a low columnar type and have a scant imperfect ciliated border.

Prostate Gland and Seminal Vesicle: More simple and regular in the structure of the acini and tubules. There is less infolding and branching of the epithelial cells. Less secretion in the tubules. Spermatozoa are present in large numbers in the seminal vesicle.

Vas Deferens: The lining cells are more vacuolated and less abundantly ciliated.

The results as given in Table X show that the prolonged administration of pituitary anterior-lobe extract, at first to the parents and then to their young, had a markedly stimulating effect upon the sex glands of Rat C, as compared with Rat B, in whose case ovarian extract was given over a period of 6 months instead of the anterior-lobe powder. Both animals were adult; nevertheless Rat C (anterior-lobe feeding) showed a sexual development considerably in excess of that of Rat B (ovarian feeding). Thus we find that spermatogenesis is much more active; the interstitial cells are more numerous; the tubules of the epididymis are larger and are filled with a secretion that contains many more spermatozoa; the prostatic gland is more hyperplastic in appearance; and the vas deferens is heavier, and its lining cells are more protoplasmic and ciliated. These, in short, are definite evidences of increased sexual development apparent even in adult life as a result of prolonged administration of anterior-lobe extract, as compared with the effect of ovarian extract. The appearance of the sex glands after ovarian administration is indicative, furthermore, of a probable inhibitive effect of the extract upon the development of the male sex glands.

THE EFFECT OF PROLONGED OVARIAN (CORPUS LUTEUM) FEEDING ON THE MALE RAT.

At the same time that observations were being made on the effect of anterior-lobe (pituitary) extract, similar experiments were being conducted to test the effect of ovarian (corpus luteum) feeding upon another rat of the same litter. The latter were carried out in order to observe the results of feeding another glandular nucleo-proteid substance *per se*, without regard to any specific action upon general bodily development or upon genital development, and incidentally to determine whether any retarding or inhibiting influence was exerted upon the development in general or sexually. The latter effect, if obtained, would seem to indicate that the ovarian extract exerts a counteracting or neutralizing influence upon the need for the secretion of the testis, and thus interferes with its development.

Two male rats were used in this observation, as any slight histological differences in the testes would be readily recognized. The condensed tabulated protocols in the following table show the effect of ovarian feeding on Male II of Litter I as compared with Male III of the same litter, which was used as the control without glandular administration. (The administration at the same time of anterior-lobe extract to the male of Pair I, Litter I (Tables VII and VIII), in another observation, makes it possible to compare the effects of anterior-lobe and ovarian feeding.)

Ovarian feeding was begun to Male II on March 8, 1913, when the animal was 5 weeks (accurately, 36 days) old, and was continued for 42 days, or until April 19 (*cf.* Table XI), when the right testis was removed surgically without sacrificing the animal. The right testis of the control had been similarly removed on April 19. Both glands were at once weighed and fixed in formalin and later sectioned for histological comparison. The feeding of ovarian extract was then continued to Male II until August 30, making a total period of feeding of 5 months and 3 weeks. On this date both animals were sacrificed and the remaining left testis was removed from each, preserved and studied comparatively. Thus we were able to make two comparative observations on the testes, one early in the period of feeding and the other at the age of 7 months. The dosage of the ovarian extract, by weight, was the same as the dosage of anterior-lobe extract to the male of Pair I, namely, 0.1 gm. daily for 2 weeks and then 0.05 gm. until the end of the experiment.

In comparing the summarized protocols, it is seen that the prolonged feeding of corpus-luteum extract over a period of 6 months had the following effect:

Whereas, at the beginning of the observation, the control animal was considerably the heavier (5.5 gms.), nevertheless the ovarian-fed male soon overtook the control in weight (*cf.* under April 13) and at the end of the experiment weighed 15.6 gms. more than the control (*cf.* August 10), owing in large part, undoubtedly, to an early and greater deposit of fat subcutaneously and retroperitoneally. This is in keeping with results obtained previously (Tables II and IX).

In spite of the greater body-weight of the ovarian-fed male, the testis is smaller in gross and the weight of the gland is less, not only absolutely but in proportion to the body-weight. Thus, on April 20 the weight of the right testis of the ovarian-fed male, per 100 gms. of body-weight, was 0.945 gms. as compared with 1.14 gms., the weight of the right testis of the

TABLE XI.—PROTOCOLS OF TWO MALE RATS OF LITTER I, ONE OF WHICH (MALE II) RECEIVED OVARIAN (CORPUS LUTEUM) EXTRACT OVER A PERIOD OF FIVE MONTHS AND THREE WEEKS, THE OTHER, (MALE III) BEING USED AS THE CONTROL.

LITTER I.	
Date.	Male II. Ovarian (corpus luteum) feeding for 5 months and 3 weeks. Age at autopsy, 7 months.
Mar. 7	Weight, 28.5 gms.
Mar. 18	Weight, 56.5 gms.
Mar. 23	Rat gaining rapidly in weight. Testes and scrotum quite large.
Mar. 30	A large rat. External genitalia in relation to body size not very large.
Apr. 13	Weight, 103.1 gms. Has overtaken the control in weight. External genitalia have not developed in proportion to the general growth of the body.
Apr. 20	Weight, 104.8 gms. Right testis removed (Apr. 19) and placed in formalin for comparison, at this early stage, with the testis of the control male. Weight of right testis, 0.990 gm. Appears smaller and feels less firm than the testis of control male. Tunica albuginea is slightly more vascular. Fur is less coarse.
May 17	Weight, 177.1 gms. A larger, more vigorous rat than control. Has considerably overtaken the control animal in weight, apparently owing to a greater deposition of fat.
May 25	Weight, 250.9 gms. Animal has been gaining rapidly in weight. Testis smaller than that of control.
June 1	Weight, 250.9 gms. Animal has been gaining rapidly in weight. Testis smaller than that of control.
July 27	Weight, 250.9 gms. Animal has been gaining rapidly in weight. Testis smaller than that of control.
Autopsy.	
Aug. 10	Weight, 229.3 gms. More subcutaneous and retro-peritoneal fat than in control. Weight of left testis, 1.930 gms. Smaller on gross inspection and by weight, although in general this animal is considerably heavier than the control. Weight of left testis after fixation and clearing in oil, 1.460 gms. Weight of seminal vesicles, prostate gland and bladder, 1.770 gms. (after fixation and clearing in oil).
	Weight, 205.7 gms. Less fat generally than Male II. Weight of left testis, 2.30 gms. Larger on gross inspection and by weight than testis of Male II, though this animal is considerably smaller than Male II, receiving ovarian extract. Weight of left testis after fixation and clearing in oil, 1.720 gms. Weight of seminal vesicles, prostate gland and bladder, 1.540 gms. (after fixation and clearing in oil).

control; and on August 10 the weight of the left testis of the ovarian-fed animal was 0.610 gm. as compared with 0.878 gm., the weight of the left testis of the control. Although the combined weight of the seminal vesicles, prostate gland and bladder is only slightly greater in the control animal (1.770 gm.) nevertheless, when considered in relation to the body-weight, the difference per 100 gms. of body-weight is far more marked. There seems to have been a definitely adipose condition of the whole body of the male produced by the feeding of corpus

luteum extract. This corresponds with results previously recorded (Tables II and IX). The condition may be compared to a sort of emaciated state, and it is probable, furthermore, that the internal as well as the external secretions of the testis have been inhibited, or that the demand for the production of these secretions by the testis has been neutralized by the feeding of the ovarian extract. This would explain the greater body-weight and the diminished size and development of the sex glands.

It is interesting also to note that the growth of the external genitalia both of the ovarian-fed animal and of the control was less rapid than in the male of Pair I of the same litter, which received anterior-lobe extract in connection with another experiment (cf. Table VII).

The gross testicular structure is coarser, and the tubules, even to the naked eye, are larger in the control than in the ovarian-fed animal. The fur of the ovarian-fed animal is softer and more delicate.

It is apparent, then, from the above facts, that the feeding of corpus-luteum extract to the male rat produces an increased body-weight, due to the general deposition of fat, and that it has a definitely retarding influence upon the growth and development of the genital system. This is especially evident when we compare the results obtained from the feeding of anterior-lobe (pituitary) extract under the same conditions.

The succeeding two tables give the histological findings in the testis, epididymis, seminal vesicles and prostatic glands of the ovarian-fed male and the control. In the first of these tables (Table XII) the right testes of the two animals, which were removed surgically after 42 days of ovarian feeding to Male II, are compared. In Table XIII the findings in the remaining left testis of each rat at autopsy at the age of 7 months are given. Thus, we have, then, the results obtained by feeding corpus-luteum extract over a short period of 42 days and after a long period of 5 months and 3 weeks.

TABLE XII.—COMPARATIVE HISTOLOGICAL FINDINGS IN THE RIGHT TESTIS OF MALE II, LITTER I, (OVARIAN FEEDING FOR FORTY-TWO DAYS) AND IN THE RIGHT TESTIS OF MALE III, LITTER I (CONTROL, RECEIVING NO GLANDULAR EXTRACT).

LITTER I.	
Male II.	Male III. Control.
Ovarian feeding for 42 days, begun when animal was 5 weeks old. Right testis removed at the age of 2 1/2 months.	No glandular administration. Right testis removed at the age of 2 1/2 months.
Weight of right testis, 0.990 gm. Spermatogenesis fairly well advanced. Active karyokinesis. Tubules in large part contain spermatozoa and spermatozoa in smaller number than in control. Many tubules show arrest at karyokinesis and only one or two cell rows; some of these tubules have an atrophic appearance. Lining less firm and contains fewer spermatozoa. Interstitial cells few, but and there is fat in large amount.	Weight of right testis, 1.140 gms. Spermatogenesis definitely farther advanced, practically complete. All tubules contain spermatozoa and show active karyokinesis. Lining of the tubules mostly contains a considerable amount of secretion, spermatozoa and free cells.
Epithelium smaller than in control. Fewer spermatozoa and more arrested cells than in control. Tubules thin and atrophic. Lining less firm and contains fewer spermatozoa. Interstitial cells few, but and there is fat in large amount.	Epithelium larger. Spermatozoa numerous. Tubules thick and firm. Lining of the tubules contains a considerable amount of secretion, spermatozoa and free cells.

TABLE XIII.—COMPARATIVE HISTOLOGICAL FINDINGS IN THE REMAINING LEFT TESTIS OF MALE II, LITTER I, (OVARIAN FEEDING FOR FIVE MONTHS AND THREE WEEKS) AND IN THE LEFT TESTIS OF MALE III, LITTER I (CONTROL, WITHOUT GLANDULAR ADMINISTRATION).

LITTER I.

Male II. Ovarian corpus luteum feeding for 5 months and 3 weeks, beginning when animal was 5 weeks old.	Male III. Control. No glandular administration
Left testis at autopsy at the age of 7 months.	Left testis at autopsy at the age of 7 months
Weight of left testis, 1.930 gms. Spermatogenesis moderately active. The tubules contain relatively few spermatozoa. The spermatogenic cells are less closely packed and in many places are arranged in fewer cell rows. The lumina of the tubules on the whole are not filled with free cells and secretion.	Weight of left testis, 2.340 gms. Spermatogenesis very active. All the tubules contain a great many sper- matozoa and intermediate cells. The tubules are lined with many rows of cells in compact arrange- ment, and most of them are filled with spermatozoa, free cells and secretion.
Interstitial cells are few in number and with a scant amount of proto- plasm, which gives them an atrophic appearance.	Interstitial cells are definitely more numerous and larger and occur in larger groups than in Male II.
Epididymis: Lumina of the tubules are large, and in many instances contain little or no secretion. The lining cells are of the low columnar type and without a ciliated border. In some tubules spermatozoa are present in mod- erate numbers, in others they are absent altogether. There are very few free cells in the tubules.	Epididymis: The tubules are very nearly of the same sizes as in Male II, but are filled and distended with secretion containing enor- mous numbers of spermatozoa. There are no tubules without great numbers of spermatozoa. The cells lining the tubules are larger than in Male II, and non- ciliated. Very few free cells are seen in the tubules.
Seminal Vesicle: Made up of large simple tubules, lined with low columnar epithelium. There is very little secretion in the tubules, in which no spermatozoa are seen.	Seminal vesicle consists of large tubules with wide lumina, as a result of being filled with secre- tion. The lining epithelium is, in consequence, thinner and lower. There is more infolding and irregularity of the walls, indicat- ing proliferation of the lining cells.
Prostate Gland: Simple acini with a small amount of secretion and no spermatozoa.	Prostate gland shows evidences of proliferation; also lymphoid cell accumulation. No spermatozoa seen.

From the two foregoing tables it is seen that the feeding of corpus-luteum extract over a brief period of 12 days and over a longer period of 5 months and 3 weeks had the following effect upon the male sexual system:

The gross size and weight of the testis, both absolutely and in proportion to the body development, is less than in the control. Spermatogenesis is not so active, and as a consequence spermatozoa are less numerous. The interstitial cells of the testis are fewer in number and have a scantier protoplasm and a more atrophic appearance. The epididymis is smaller, it looks less active and contains less secretion and fewer spermatozoa and free cells in the lumina of the tubules. The cells lining the latter are of a lower columnar type and are not as abundantly supplied with ciliated borders. Moreover, at autopsy the seminal vesicles and prostatic gland of the ovarian-fed male appear smaller, less active and contain less secretion than those of the control (Fig. 13).

From these facts we see that the retarding influence of ovarian extract upon the male sexual development is exerted throughout the life of the animal, and not only upon the testes but also upon the entire genital system.

DISCUSSION OF RESULTS.

It is the anterior-lobe element in the secretion of the pituitary gland that is to be looked upon as supplying the principle responsible for the stimulating and activating influence upon sexual development and function. This explains why, in the

disease acromegaly—now generally believed to be due to an over-function of the anterior lobe of the pituitary gland consequent upon adenomatous hyperplasia—we find in the early stage an exaggerated sexual activity and libido, and in the late stage, that corresponds with pituitary involution and inactivity, a disappearance of the sexual function. The sex glands in this late stage show, histologically, atrophy and various forms of degenerations. Additional light is thrown on those experimental and clinical conditions of underdevelopment and genital inactivity and hypoplasia occurring in conditions of experimental removal of the anterior lobe of the pituitary, and in clinical conditions of under-function consequent upon disease of the pituitary itself, or of its neighborhood, compromising the function of the gland.

The belief, furthermore, that a deficiency of posterior-lobe (and pars-intermedia) secretion is responsible for the genital hypoplasia seen in many clinical and experimental disorders of pituitary function, as suggested by Biedl,²⁸ seems untenable, in view of the results obtained by the feeding of posterior-lobe extract to rats. The latter extract certainly does not stimulate, but would seem even to retard, sexual development; consequently its loss should not be associated with genital hypoplasia. By "posterior-lobe" extract, as used in these experiments, we mean as well the extract of the pars intermedia, that anatomical division of the pituitary gland which closely invests the posterior or nervous lobe proper and which would naturally go with the latter when the gland is divided into its two main divisions of anterior and posterior lobes. Extracts made from the posterior lobe would thus ordinarily contain pars intermedia substance. Furthermore, it seems to have been shown beyond doubt that the secretion from the pars intermedia travels through the meshes of the posterior lobe and therefore would be contained in the latter. (Herring,²⁹ Cushing and Goetsch,³⁰ Cow.³¹)

It seems probable that in conditions interfering with the normal function of the pituitary gland, both the anterior and posterior lobes are involved, and that we therefore see in the corresponding clinical states symptoms due to disturbances in both lobes. We know that a deficiency in posterior-lobe secretion is followed by a tendency to the deposition of fat and to changes in metabolism such as an increased tolerance for carbohydrates,³² and that these changes can be favorably influenced by the administration of posterior-lobe extract. The genital disturbances which are associated with these changes in clinical states should therefore be benefited by the administration of anterior-lobe extract. The carbohydrate tolerance,

²⁸ Biedl, A.: Innere Sekretion, 1913, 2te Aufl., Theil II, 187.

²⁹ Herring, P. T.: The histological appearances of the mammalian pituitary body. Quart. Journ. Exper. Physiol., 1908, I, 121-159.

³⁰ Cushing, H., and Goetsch, E.: Concerning the secretion of the infundibular lobe of the pituitary body and its presence in the cerebro-spinal fluid. Am. Journ. Physiol., 1910, XXVII, 60-86.

³¹ Cow, D.: On pituitary secretion. The Journ. of Physiol., 1915, XLIX, No. 5, 375-376.

³² Goetsch, E., Cushing, H., and Jacobson, C.: Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri. Bull. Johns Hopkins Hosp., 1911, XXII, 165-190.

which, as was stated in the paper just quoted, could be used as an index to posterior-lobe deficiency, might also serve a similar purpose in determining the degree of anterior-lobe deficiency, and thus be a guide to the dosage to be used in our gland therapy. From this it becomes evident that the best results should be obtained by giving pituitary whole gland extract in these clinical cases of under-function of the hypophysis.

As a result of the facts learned from the feeding of pituitary extract to rats, we should feel encouraged in our efforts to benefit states of ductless-gland under-function, particularly of the hypophysis, by the oral or possibly the hypodermic administration of gland extracts. Considerable success has already been obtained from such therapy. Thus, for example, a number of cases of pituitary disease, showing, among other symptoms, the characteristic sexual disturbances (amenorrhœa, and loss of *libido* and *potentia sexualis*), have been recorded by Cushing,^a in which, after administration of pituitary extracts by mouth, there has been a return in part or entirely of menstruation and of *libido* and *potentia sexualis*. In the same place, supplementary feeding after surgical procedures on the pituitary gland is recommended. Since many of the clinical conditions showing genital aplasia, adiposity and under-development combine symptoms referable to certain of the ductless glands other than the pituitary, the extract of the latter should be given to help bring about normal sexual development and activity, and with it might be given extracts of other ductless glands which would seem certainly to be involved.

And lastly, it seems likely that when we have learned the effect of administration of the different glandular extracts, such as the inhibiting effect of ovarian feeding upon the male sexual development, we could treat conditions of over-activity of one of the ductless glands with extracts of another of the endocrine series possessing an opposing or inhibiting action.

CONCLUSIONS.

I. *The dried powdered pituitary extract derived from both the anterior and posterior lobes of the gland*, when fed to young rats in excessive doses (0.1 gm. daily), causes failure to gain in weight, loss of appetite, increased peristalsis, a mild enteritis, and certain nervous manifestations, such as muscular tremors and weakness of the hind limbs. The latter symptoms are undoubtedly due to the posterior-lobe element in the whole-gland extract, for they are similarly produced by using posterior-lobe, but not by using anterior-lobe extract. Even when whole gland is fed over a short period of time, from 25 to 40 days, it causes a more rapid growth and development and gain in weight, larger nipples in the female, and a coarser, drier, harsher growth of hair than are seen in either control animals or after similar administration of ovarian (corpus luteum) extract in equivalent dosage.

The Influence Upon the Female Sex Glands.—In comparison with the development in control animals, the ovaries, tubes, and cornua of the uterus of animals fed with whole-gland

extract are larger, more vascular and œdematous in appearance, indicating increased development and activity. Even at the early age of 2½ months, from one to two months before normal sexual maturity, the ovary is matured, and shows active ovulation and Graafian-follicle formation, relatively few primordial follicles and some increase in the amount of interstitial tissue. This rather striking appearance in so young an animal gives one the impression that an early ovarian maturity has been produced by the feeding of the pituitary extract. The fimbriated end of the tube is more branched and the lining columnar cells are more ciliated, an indication of greater activity. There is marked hyperplasia of the uterine mucosa, the lining cells of which are more uniformly ciliated and active, and there is abundant gland formation in the endometrium. The appearance presented by the latter strikingly resembles in microscopic appearance the hyperplastic endometrium of early pregnancy. There is a generally increased vascularity produced in the whole sexual system. The over-development is apparent even in the muscle coat of the uterus, which is considerably thickened and is also more vascular. A somewhat similar change is produced by the feeding of corpus luteum to the female (see below, IV).

The Influence Upon the Male Sex Glands.—The testes show a considerably earlier growth and development; they are completely and permanently descended at an earlier age, and their gross weight is greater than in the control animal. This is evidenced by the extremely active spermatogenesis, with formation of spermatozoa, and by a moderate increase in the amount of interstitial tissue, at a time when the control animal is sexually still very immature. All these developmental, structural and functional changes in the sex glands of both the male and the female, produced by the feeding of pituitary extract, show an extremely selective and almost specific action of the latter upon the genital system.

II. *The feeding of pituitary anterior-lobe extract causes increased weight and greater and more vigorous body-growth and development over the control.* There is similarly an earlier and more active genital development. The fur is harsher and thicker. Loss of weight, enteritis, and nervous manifestations are not observed as in the beginning of whole-gland feeding (see above, I). As compared with the control, the animal fed with anterior lobe for only 40 days shows an earlier descent of the testes, which are also larger, more vascular and heavier, not only absolutely, but in proportion to the body-weight. The testis is mature at least as early as 2½ months, after 40 days of anterior-lobe feeding. The period of complete sexual development is shortened by at least one month, or about one-third of its normal time. Histologically, the testis at this age is mature; it shows an abnormally early and active karyoxemes, more active in fact than is seen in the testis of a normal rat at the age of from 3 to 4 months. The testis of the control at this same age is quite immature. The interstitial cells do not seem to increase in number proportionately to the increase in spermatogenic cells and spermatozoa. The epididymis contains more spermatozoa and has a more active-looking structure. The prostatic gland, seminal

^a Cushing, H.: The pituitary body and its disorders, Philadelphia, 1912, p. 318.

vessels, and vas deferens show a correspondingly early and increased development and activity. These changes produced by the feeding of anterior lobe indicate that the latter supplies the active principle in the whole gland responsible for the changes reported above, following the feeding of whole-gland extract.

After prolonged feeding of anterior-lobe extract, over a period of 8 or 9 months, the sexual instincts are early awakened, along with the early maturity of the sex glands. As a result of this, a pair of rats, after anterior-lobe feeding over a number of months, bred earlier and oftener, the female of this pair having two pregnancies in 7 months, as compared with none in the female of the control pair. The effect of anterior-lobe feeding lasts throughout the adult life of the animal. The control rat never reaches the degree of development and activity shown by the animal receiving the anterior-lobe extract. For even at the age of 10 months, after $8\frac{1}{2}$ months of anterior-lobe feeding, the latter still shows a greater, more active and mature sexual development than the control.

The feeding of pituitary anterior lobe to parent rats exerts its stimulating influence upon the offspring in intra-uterine life and during lactation, and, when the experiment is carried further, and the feeding to the young is continued after weaning, it has an even greater stimulating effect upon growth, weight and development, and causes earlier and more frequent breeding, and an increased number of offspring in the litters. The stimulating effect upon the sex glands is greater, the longer the influence of anterior-lobe administration is exerted.

III. *The extract of pituitary posterior lobe*, even after prolonged administration, does not stimulate growth in general, nor the development of the sex glands, as does anterior lobe even after a very short period. Thus, for example, there is a much less marked development of the sex glands after administration of posterior lobe for $1\frac{1}{2}$ months than after anterior-lobe administration for $2\frac{1}{2}$ months. The posterior-lobe element in the whole-gland extract has an undoubted retarding influence upon the development of the sex glands, an effect very similar to that of ovarian extract upon the testes. This is shown by the relatively incomplete development of the

testes, for example, after $8\frac{1}{2}$ months of posterior-lobe feeding. If given in too large a dose, the extract causes in the rats loss of weight, a mild enteritis and increased intestinal peristalsis.

IV. *Ovarian extract* (corpus luteum), when fed to the male, especially, causes a tendency toward the deposition of fat, not only in the body generally, but in the testes and other glands as well, with a resultant marked increase in weight. The fur is heavier and coarser than in the animal fed with the posterior-lobe extract. It does not cause an early descent of the testes. The latter are slightly heavier than those of the posterior-lobe-fed animal. This may be due, however, to an inhibiting effect exerted by the posterior-lobe extract rather than to any stimulating effect of the ovarian extract. The tendency to retardation of testicular development is possibly more definite after ovarian feeding than after posterior-lobe feeding. Corpus luteum, when fed to the female rat, is equally as stimulating as whole pituitary gland (active because of the anterior-lobe element which it contains), but not so stimulating as the equivalent weights of anterior lobe.

Following ovarian feeding there is, as compared with conditions in the control, increased development and activity of the female sex glands, increased follicle formation, a moderate increase in interstitial tissue and increased branching of the fibriated extremity of the tube. Prolonged ovarian feeding, *e. g.*, for 5 to 6 months, to the male rat, as compared with the control, has the following effect: The gross size and weight of the testes, both absolutely and in proportion to the body development, is less, and histologically the sex glands of the male show a retarded development and evidences of diminished activity. The definitely retarding influence of ovarian extract upon the male sexual development is exerted throughout the life of the animal.

Briefly then, we can say that pituitary extract (anterior lobe), when fed to young rats, has a stimulating effect upon the growth of the animal and upon its sexual development and activity. Posterior-lobe extract, when thus given, has a retarding influence. Ovarian extract (corpus luteum) has a stimulating influence upon the female, and a retarding influence upon the male, sexual development.

A CASE OF PSEUDO-HERMAPHRODISM, WITH REMARKS ON AB-NORMAL FUNCTION OF THE ENDOCRINE GLANDS.¹

By WM. C. QUINBY, M. D.

(From the James B. Brady Urological Institute, Johns Hopkins Hospital.)

Robert S. was admitted to the Brady Clinic of The Johns Hopkins Hospital on June 8, 1915, for hypospadias and undescended testicles. He was 10 years old in July, 1915.

The family history relates that one brother died at birth, and one at 7 months of age. One younger sister is living and is normal. Both parents are well; they are first cousins. The

father has a slight hypospadias with the meatus about half an inch below the apex of the glans.

Until two years of age the patient suffered from "marasmus," but otherwise has been entirely well and strong, and has had none of the exanthemata. His mentality is considered good, and he is now in the third grade, although attendance at school began only two years ago. His habits and activities are those of a normal boy; he spurns girlish pursuits, and much prefers such games as foot-ball. The pubic and axillary

¹ I take pleasure in extending my thanks to Dr. Hugh H. Young for permission to operate on this patient and to report the case.

hair has been present for four years. The voice has been "coarse" and the hands and feet "stubby." Since birth the urethra has opened at the base of the penis and the testes have not descended. There is an entire absence of any history of abdominal pain or crises suggestive of retained menstruation; there has never been any bleeding from the penis. *Libido* has not appeared as yet.

Physical examination finds the general bodily condition and color excellent. The musculature is well developed. The head is rather large, with prominent frontal regions, and the shoulders, though broad, are markedly stooping. The forehead is of moderate height; the face is broad; the lips are thick; the nose is flat. The hair, dark brown in color, is rather coarse and is lacking over each lateral frontal region. The eyebrows are more sparse in their outer portions than toward the root of the nose. The eyes, ears, and mouth are normal. The ears show no stigmata and the upper central incisors are no broader than the other incisor teeth. The palate is moderately high. There is a considerable amount of fine hair on the upper lip; the axillary and pubic hair is abundant, the latter showing the female type of distribution. The hands are broad and short, the finger-nails have been bitten. The skin over the body is somewhat harsh. There are no abnormal deposits of fat. On examination, the heart, lungs, and abdomen are entirely normal. The breasts are undeveloped and of the male type. Very careful palpation shows no sign of any abnormal abdominal mass. There is no unnatural pigmentation of the skin. The growth of hair below the knee on each leg is in marked excess.

On examination of the genitalia, the phallus is found to be represented by an organ 5 cm. long, curved markedly toward its ventral surface. There is a well-developed prepuce drawn into folds on the dorsum, but not uniting completely in the mid-line on the ventral side. This covers the glans, which is well developed except for the meatus, which is replaced by a ventral groove. At the base of this structure, between it and the slightly prominent mons, the skin rises in a fold, and encircling the phallus, extends downward on either side to form the bifid scrotum or labia majora. No testes or spermatic cords are to be felt anywhere. When the glans is drawn upward, the opening of the urethra is seen at a point corresponding to the peno-scrotal junction. From this to the tip of the glans the middle line shows a longitudinal gutter covered by striæ of mucosa. The perineum from meatus to anus is smooth and without trace of depression. There is nothing to suggest labia minora. An abundance of hair is present, and the skin of the perineal region and adjacent thighs is harsh and coarse.

There is a definite lack of equilibrium on the part of the superficial vaso-motor system. The hands are cold, clammy, and often of dusky hue; the skin of the body shows a marked on cooling, and the patient blushes very readily. All the reflexes are lively, but there is no cremasteric reflex.

Rectal examination shows an apparent absence of the prostate, although in the region above this area there is felt a small mass which is about 2 cm. long and 1 cm. broad, not movable and only slightly movable.

Radiographs of the skull, chest, abdomen, pelvis and hands are entirely normal. The urine is normal, and the ingestion of 150 grams of dextrose caused no glycosuria. The phenol-sulphonephthalein output was 60 per cent during the first hour. The Wassermann test was negative.

Blood-pressure: Systolic, 115; diastolic, 90.

Blood count: Red blood cells, 5,128,000; white blood cells, 7,780.

Differential count:

Polymorphonuclears	75.5%
Small mononuclears	12.0%
Large mononuclears	4.5%
Transitional	4.0%
Eosinophiles	4.0%
Blasts	none
	100.0%

Pharmacodynamic tests: Following the injection of five minims of adrenalin 1:1000, the systolic blood-pressure rose from 115 to 135 in the following 15 minutes, again reaching normal in 25 minutes. There were a few extra systoles during this time, but no tremor, no change in the pupils, and no subjective signs. The pulse count reached 165, 10 minutes after the injection. The injection of seven minims showed nothing further.

The eyegrounds and the perimetric fields were normal. Hearing was normal.

Measurements:

Weight	34.0 kilos.
Height, standing	146.0 cm.
Height, sitting	80.0 cm.
Span of arms	144.0 cm.
Girth of chest, at rest	73.5 cm.
Girth of chest, on inspiration	77.0 cm.
Girth of chest, on expiration	70.0 cm.
Length of head	18.3 cm.
Width of head	15.0 cm.
Height of face	10.5 cm.
Width of face	12.5 cm.
Height of palate to incisor teeth	4.5 cm.
Circumference of neck below thyroid cartilage	31.5 cm.
Circumference of abdomen at umbilicus	67.0 cm.
Distance between anterior superior spines	21.0 cm.
Distance between iliac crests	22.5 cm.
Distance between femoral tuberosities	26.5 cm.
Distance between top of symphysis and top of sacrum	17.0 cm.
Distance between top of symphysis and umbilicus	13.9 cm.
Distance between umbilicus and sternal notch	35.0 cm.
Distance between acromion processes	33.0 cm.
Distance between anterior superior spine and bottom of patella (left)	42.0 cm.
Distance between anterior superior spine and bottom of patella (right)	41.5 cm.
Distance between anterior superior spine and internal malleolus (left)	73.0 cm.
Distance between anterior superior spine and internal malleolus (right)	71.9 cm.
Length of feet (each)	28.0 cm.
Circumference of thigh (each)	42.0 cm.
Circumference of knee (left)	29.0 cm.
Circumference of knee (right)	30.0 cm.
Circumference of calf (each)	28.0 cm.

Distance between acromion and olecranon (left).....	30.0 cm.
Distance between acromion and olecranon (right)....	31.0 cm.
Distance between olecranon and ulnar styloid (each)...	20.0 cm.
Circumference of biceps (left).....	21.0 cm.
Circumference of biceps (right).....	22.5 cm.
Circumference of forearm (left).....	20.0 cm.
Circumference of forearm (right).....	21.0 cm.
Circumference of wrist (each).....	14.0 cm.
Circumference of hand (left).....	18.0 cm.
Circumference of hand (right).....	19.0 cm.

It will be of interest to compare some of these measurements with the averages obtained by Porter in his examination of over 34,000 school children.² We can thus roughly determine the age and sex which our patient most nearly approximates.

Weight most nearly corresponds to Porter's.....	Boy of 13.
Height standing most nearly corresponds to Porter's....	Girl of 13.
Height sitting most nearly corresponds to Porter's.....	Boy of 15.
Span of arms most nearly corresponds to Porter's.....	Boy of 13.
Girth of chest most nearly corresponds to Porter's.....	Boy of 14.
Length of head most nearly corresponds to Porter's....	Boy of 13.
Width of head most nearly corresponds to Porter's.....	Boy of 16.
Height of face most nearly corresponds to Porter's.....	Boy of 15.
Width of face most nearly corresponds to Porter's.....	Boy of 13.

Although this is a rough comparison, it is interesting in showing that most of the measurements fall nearest to those of boys of from three to six years older than our patient.

An operation was performed on June 14, 1915, to better the hypospadiac condition and to search for the supposed testicles and bring them down. No trace of the spermatic cord could be found in the inguinal canal. On entering the abdomen I discovered an infantile uterus with tubes and ovaries of normal appearance. An ovary, with an adjoining portion of its tube, was excised for histological examination.

HISTOLOGICAL REPORT.

The specimen consists of an ovary 2.5 x 1.3 x 1.7 cm., together with about 5 cm. of tube, bearing normal fimbriae. Running from one side of the ovary is a layer of very thin tissue, apparently a bit of the broad ligament, containing on one surface a small, very flabby mass in the position of the parovarium. The surface of the ovary is smooth, and on section it is seen to contain numerous areas varying in size, presumably follicles. The larger of these contain bloody fluid, the smaller watery fluid.

Microscopic Examination.—Sections of the ovary show a typically normal structure. Graafian follicles contain ova in various stages of development. No corpora lutea are seen, although there is in one area a splendidly preserved corpus fibrosum. A careful search failed to show any abnormal elements.

The Fallopian tube shows the usual papillary-like foldings of mucosa with normal epithelium.

The parovarium shows numerous tubules, thin-walled, and having a single layer of epithelium.

² W. T. Porter: The Growth of St. Louis Children. Trans. St. Louis Acad. Sci., 1895, VI, 263.

DISCUSSION.

It is evident from the foregoing that we are dealing here with a case of atypical *sexe-ensemble*, more commonly, though less correctly, called pseudo-hermaphroditism. The sex of an individual must always be determined by the nature of the gonad, regardless of the presence of abnormalities either of other parts of the genital system or of the secondary sexual manifestations of the body as a whole. Consequently, this patient is of the female sex; and this in spite of so many secondary characteristics of the opposite, male, sex.

In the sphere of the internal genitalia the development has followed a normal course; uterus, tubes, and ovaries are present, and are normal so far as examined. The external genitalia, however, show many deviations from the normal female type. The urethra opens in its usual position, but the clitoris is much overdeveloped, closely resembling a penis of the hypospadiac sort, and there is no external trace of vagina. It is to be presumed, on morphological grounds, that a rudimentary vagina exists, but attempts to examine the posterior urethra with an endoscope were without conclusive result because of the small size of the structures.

The patient, therefore, belongs to the class of female pseudo-hermaphrodites of the external type. But though the external genitalia are atypical, it is in the domain of the secondary sex characteristics that the most marked deviations are found. The voice, the hair on the face, the general bodily habitus, and the mental processes are all of the heterologous male type. Indeed, on adding the precocious hair development to the above appearances, this individual seems to possess a degree of maleness considerably greater than that usual in normal children at 10 years of age. The comparison with the normal averages of Porter given above bear out this impression. Only the distribution of the pubic hair, and the configuration of the thighs remain of the female type. In this respect the case is unusual, for though over two thousand case reports of pseudo-hermaphrodites are to be found in the literature,³ those bearing the male gonad are about ten times as common as those bearing the female; and in these latter only a few reports describe such complete presence of the heterologous secondary manifestations of sex.

Relations between the Endocrine Glands and Sex Aberrations.—There has been of late years a rapidly increasing amount of evidence, both experimental and clinical, tending to show that the proper development of those attributes which constitute the *sexe-ensemble* is dependent on normal activity of the endocrine system. Though it is to be doubted that internal secretory processes play any rôle in the primary determination of the sex of the gonad itself, it is certain that such processes are responsible for the normal progress of events from a very early age. The present teaching is well stated by Barker⁴ when he says: "We are simultaneously, in

³ Neugebauer: Hermaphroditismus beim Menschen. Leipzig, 1908; also, *Jahrb. f. sexuelle Zwischenstufen*. Bd. V.

⁴ Barker, L. F.: On abnormalities of the endocrine functions of the gonads of the male. *Am. Jour. Med. Sci.*, 1915, CXLIX, 1.

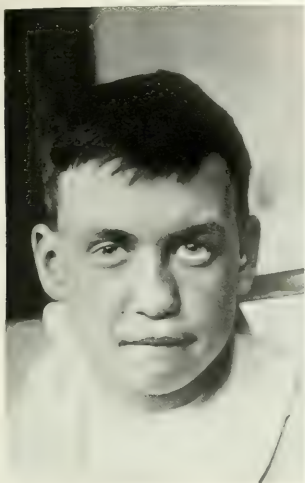


FIG. 1.



FIG. 2.

Figs. 1 and 2.—Front and side views of head. Note the shape of the calvarium; the flat nose and thick lips; the hair distribution in eyebrows and on upper lip.



FIG. 3.—Front view of body. Note the male shoulders; the broad, short hands; the pubic hair with horizontal upper edge; the rather feminine rotundity of thigh, and the hypertrichosis of legs.



FIG. 4. Front view of trunk. Note the typical male breast and shoulders.





FIG. 5.—Lateral view, with the patient standing, to show the general poise and round shoulders.



FIG. 6.—Right hand; to show the severely bitten finger nails and the configuration—the *main en large* of Marie.



FIG. 7.—The external genitalia. Note the phallus with prepuce, and labia majora simulating a bifid scrotum; also the extensive growth of hair and the coarse skin.



FIG. 8.—The external genitalia with the labia separated and the phallus raised. The median furrow of mucosa is seen, bearing the urethral opening, represented by a dark spot half-way between the examining fingers and thumbs. Note the entire absence of vagina.

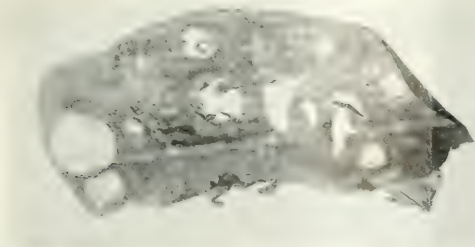


FIG. 9.—Low-power magnification of ovary, to show follicles.

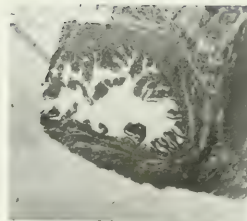


FIG. 10.—Low-power magnification of tube in cross-section.

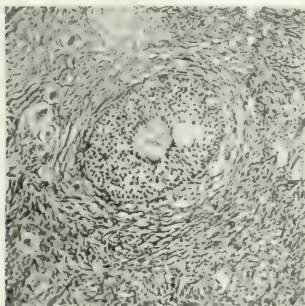


FIG. 12.

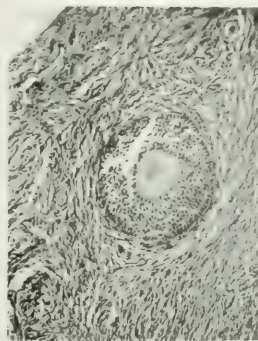


FIG. 13.

Figs. 12 and 13.—Graafian follicles containing ova in various stages of development.

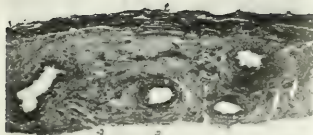


FIG. 11. Low-power magnification of parovarium showing the characteristic epithelium-lined tubules.

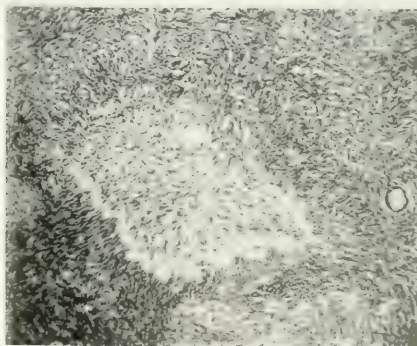


FIG. 14. A corpus fibrosum showing healing after rupture of a follicle.

a sense, the beneficiaries and the victims of the chemical correlations of our endocrine organs."

Space will not permit a detailed consideration of the probable physiological action of each of the hormone-producing organs. We must, however, consider at some length the relation of the adrenal cortex to sex, for abundant and convincing evidence of its importance in this regard is at hand.

It will be recalled that the adrenal cortex is developed from the Wolffian ridge—that is, from the same rudimentary tissue as is the sex-gland—whereas the medulla is of neuro-ectodermal origin, as are also the sympathetic ganglia. During intra-uterine life the gland is about equal in size to the kidney. This is due to an enlargement of the inner portion of the cortex—the so-called fetal cortex—which begins to degenerate at or soon after birth. The medullary portion of the gland produces adrenalin; the cortical area is considered to be the source of a hormone that influences growth, nutrition, and especially the reproductive organs.⁵ Clinical and pathological evidence demonstrates the remarkable effect that lesions of the adrenal cortex exert on the various factors constituting sex. Pathologically such lesions may consist of simple hyperplasia, or there may be found hypernephromata. During pregnancy in human beings, and in some animals during heat, hyperplasia seems to be a normal process. Much light has been shed on this whole subject by the admirable communication of Bulloch and Sequeira;⁶ of Fibiger;⁷ of Apert;⁸ of Launois, Pinard, and Gallais;⁹ and of Glynn;¹⁰ and most recently by the exhaustive review of the literature in the article of Hofstätter.¹¹

The clinical manifestations of disturbed function of the adrenal cortex vary according to the age at which the disturbance arises. Apert makes five groups: (1) Cases in

which the disturbance occurs in embryonal life, and is associated with a greater or less degree of hermaphroditism. (2) Cases with normal sex organs, but with too early and profuse development of bodily hair (hypertrichosis). (3) Precocious puberty. Overdevelopment of hair and fat, but without trace of hermaphroditism. (4) After puberty. The menses disappear; the bodily fat increases as does the hirsuties. (5) Later cases showing loss of hair, and overgrowth of fat at the time of the menopause.

Glynn's article deals with the relation of adrenal cortical tumors to sex. He finds that adrenal cortical hypernephromata are accompanied by sex abnormalities in children almost invariably. They are usually so accompanied when occurring in adult women before the menopause; whereas after the menopause, and in adult males, they are never so accompanied. In pseudo-hermaphrodites, adrenal rests (or bilateral hyperplasia) are much more common in the individuals that bear the female gonad. Tumors occurring in males after birth may cause marked bodily overdevelopment; so that a child suffering from this condition may have the appearance of an "infant Hercules." This condition may also be associated with true sexual precocity.

The sexual changes seen in acromegaly, and after experimental interference with the pituitary body,¹² furnish evidence that this gland also exerts an action over some of the sexual characteristics. It may therefore be supposed that there exists some interrelation between the pituitary body and the adrenal cortex, though at present the evidence of such is largely speculative.

In view of the fact that such cases of endocrinopathy as the one here reported are almost surely due to an adrenal lesion, careful search was made for clinical evidence bearing on this special point. None could be found, however. The pharmacodynamic tests were negative, and no palpable tumor could be made out. Likewise, careful examination of stereoscopic radiographs of the skull showed a perfectly normal sella turcica.

CONCLUSION.

A case of female pseudo-hermaphroditism of the external type is reported, showing unusual accentuation of the secondary sex characteristics of the male. Judging from the literature, such cases represent an endocrinopathy of the adrenal cortex, surely; possibly also of the pituitary body.

¹² Crowe, Cushing and Homans: Experimental Hypophysectomy. Johns Hopkins Hosp. Bull., 1910 XXI, May.

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The Hospital Bulletin contains details of hospital and dispensary practice: abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXVII is now in progress. The subscription price is \$2.00 per year.

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⁵ Vincent, S.: *Ergebnisse d. Physiol.*, 1910, X, 581.

⁶ Bulloch and Sequeira: On the relation of the suprarenal capsules to the sexual organs. *Trans. Path. Soc. Lond.*, 1905, LVI, 159.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

OCTOBER 18, 1915.

The meeting was called to order by the president, Dr. W. S. Thayer. The election of officers for the ensuing year was then held. Dr. Hugh H. Young was elected president and Dr. W. A. Baetjer, secretary.

1. The Ideal Operation for Aneurisms of the Extremity. B. M. BERNHEIM.

To appear in full in a later issue of the BULLETIN.

2. On the Toxicity of Various Commercial Preparations of Emetin Hydrochlorid. (Abstract.) R. L. LEVY and L. G. ROWENHART.

The widespread use of emetin hydrochlorid in the treatment of amebic dysentery and of pyorrhea alveolaris makes desirable more precise knowledge of the toxicity of the commercial preparations employed. Two cases occurring in the medical service during the past year forcibly emphasize this fact.

The first case was that of a syphilitic man of 56, who, because of a diarrhea, supposedly amebic in origin, was given, hypodermically, 29 grains of the drug over a period of 20 days. He died ten days after discontinuing the emetin treatment, with evidences of acute renal insufficiency accompanied by acidosis. At necropsy, syphilitic aortitis, chronic indurative colitis and broncho-pneumonia were the only findings of importance.

In the second case, 2 grains were given hypodermically, during a 4-day period, to an undernourished anemic woman suffering from a severe grade of pyorrhea and gingivitis. A severe diarrhea developed, with pus and blood in the stools, followed by a toxic delirious psychosis. On discontinuation of the emetin, recovery ensued.

A dog was injected subcutaneously with some of the same preparation employed in the second case, and died with a hemorrhagic gastro-enteritis, after three doses of 10 mg. each, given on successive days.

Subsequently, studies were made on 62 animals, the series including dogs, cats and rabbits. Five commercial preparations were

investigated. Injections were made both subcutaneously and intravenously. The following facts were brought out:

1. Various commercial preparations differ widely in toxicity. The therapeutic dose (mg. per kg.) closely approximates that necessary to produce toxic symptoms.

2. When intravenously administered, emetin is a powerful cardiac poison, causing at times fibrillation of the ventricles, from which the animals may recover. It is also a circulatory and respiratory depressant.

3. In fatally poisoned dogs, the characteristic lesion is a hemorrhagic gastro-enteritis. Lesions in cats and rabbits are slight and inconstant.

4. The factors of blood coagulation are disturbed in poisoned animals.

5. There is found no evidence of renal insufficiency; a slight terminal acidosis is present.

On reviewing the reported cases in which ill effects have followed the clinical use of emetin, it is apparent that diarrhea is an early toxic manifestation and that peripheral neuritis is one of the most frequently observed sequelæ, even after the administration of therapeutic doses.

As a result of these observations, it is suggested that emetin preparations be employed with caution. It is desirable that the drug be given subcutaneously, in courses, at intervals of several days or a week. A third of a grain three times a day, for a week or ten days, is usually a safe dosage in amebic infections. According to Bass and Johns, half a grain daily for from three to six days suffices in pyorrhea. Large doses should be avoided. Intravenous injections should be employed only in extreme cases. If this mode of administration seems imperative, small doses, well diluted (gr. ss. in 100 cc. salt solution) should be slowly given, and the blood pressure should be carefully observed during the injection.

3. A Method for the Determination of Plasma and Blood Volume. (Abstract.) N. M. KEITH, L. G. ROWNTREE and J. T. GERAGHTY.

In brief, the method consists in the introduction directly into the circulation of a given quantity of a non-toxic, non-dialysable dye, vital red, and the taking of specimens of blood within a few minutes for determining the degree of dilution of the dye.

The patient is weighed (stripped) and the amount of dye to be injected determined on the basis of 3 mg. per kilo of body-weight. Before injection, a small sample of the patient's blood is withdrawn and the plasma thus obtained is used in the preparation of the standard solution. At intervals of three and six minutes after the injection, specimens of blood are taken and the degree of dilution of the dye is determined colorimetrically by comparison with the standard solution. The latter solution is prepared by diluting the number of cubic centimeters of the dye injected in the number of cubic centimeters corresponding to 4 per cent of the body-weight in grams, the diluent employed consisting of one part of the patient's plasma to three parts of normal saline. From the reading obtained on the colorimeter, a simple calculation gives the plasma volume. By employing the hæmatocrit values, the total blood volume is readily calculated.

The loss of the dye from the circulation during the short period of the test is very small. The dye cannot be found in the tissues and evidence from numerous experiments prove that little, if any, is taken up by the red or white blood cells. In dogs, traces of it appear in the urine and in the lymph flowing from the thoracic duct at the end of ten minutes. The fate of all the dye has not been determined, but considerable amounts can be found in the plasma for three or four days following the injection of 3 mg. per kilo.

Repeated determinations on the same individual yield practically identical results, the maximal variation being within 5 per cent.

The average figures in normal individuals indicate that the plasma volume is 50 cc. per kilo, or one-twentieth of the body-

weight, while the total blood volume amounts to 85 cc. per kilo, or about one-twelfth of the body-weight.

Clinical studies show that in obesity, as previously observed by Haldane and Smith, the blood volume is much below that of the average normal individual. In diabetes and in essential hypertension, the values obtained are within normal limits. In pregnancy there is a large increase in the blood mass, which does not disappear until from seven to ten days after delivery.

DISCUSSION.

L. F. BARKER: It has long been desirable to have a method that would permit us accurately to determine the blood volume. Dr. Rowntree has referred to the methods that have been in use. None has been wholly satisfactory. Still the results that were obtained by some of them would indicate that Cohnheim was wrong in asserting that plethora and oligæmia do not occur. If this new method is accurate, as it seems to be, we have in our hands a means of studying the plethoras and the oligæmias carefully. I have not read the article, so do not know whether cases of polycythæmia, nephritic hydræmia and chlorosis were dealt with. These are cases in which an outspoken plethora has been found to exist.

In polycythæmia rubra, a blood volume at least twice as great as normal has been found. It is a remarkable thing that with the plethora in polycythæmia, in which the volume of blood is doubled and there is an increased viscosity of the blood, the heart is not hypertrophied. One reason for this would appear to be that the blood corpuscles are smaller than normal in polycythæmia. More important still is the fact that the minute volume of the heart is diminished, so much so that the duration of the total circulation is really prolonged. The result is that the heart does not have more work to do, although it would seem *a priori* that it would have more to do. In chlorosis, sometimes as much as three times the normal blood volume has been reported to be present.

On the other hand, in the oligæmias, in which there is a diminished quantity of blood, some interesting observations have also been made. Dr. Rowntree has referred to conditions in which there is a decrease of red cells and an increase of plasma. In starvation, there is a true oligæmia, and sometimes also in chronic inanition and emaciation. Perhaps the most interesting group of oligæmias is that of the so-called "pseudo-anæmias." Anyone who has made many observations upon pale-looking patients has been struck with the fact that in many of them there is a normal amount of hæmoglobin and a normal blood count. The question has been raised in such cases: Is there a true oligæmia? or, Is some other factor responsible for the pallor? Sahli thought that a good many of the cases could be explained by a change in the distribution of the blood in the body, without change in the blood amount, the skin and mucous membranes having a lessened supply; or that the transparency of the skin and mucous membranes was less than normal, so that the blood pigment did not show through. However, studies by Morawitz and others indicate that in many of these pseudo-anæmias, especially in the tropical pseudo-types, there is a true oligæmia.

The opportunities for the application of this method described to-night are manifold. We may now approach the study of plethora on the one hand, and of oligæmia on the other, with the hope of solving some of the questions that have hitherto been in dispute.

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A DISCUSSION OF ACIDOSIS.*

WITH SPECIAL REFERENCE TO THAT OCCURRING IN DISEASES OF CHILDREN.

By JOHN HOWLAND, M. D., and W. McKIM MARRIOTT, M. D.

(From the Harriet Lane Home and the Department of Pediatrics of The Johns Hopkins University.)

The term acidosis is one that, at the present time, is very generally and very loosely employed in clinical medicine. It is used, for the most part, to indicate that acetone bodies have been found in the urine by qualitative tests. In descriptions of most of the recorded cases, however, those symptoms that we may look upon as important for the diagnosis of acidosis are not to be found. It is assumed that the acetone bodies are very abnormal and that their presence signifies an unusual complication in the course of disease. Whereas, we may, in many instances, liken the mere presence of acetonuria to fever; for it occurs in most of the infectious diseases of children with much the regularity that fever does. We do not look upon moderate fever associated with infectious processes as unusual or dangerous, nor should we look upon the acetone bodies in the urine as unusual or dangerous. Hyperpyrexia may, however, develop and in itself be dangerous or fatal. So, too, a production of the acetone bodies may in itself determine a fatal outcome.

But the quantitative difference between the mere presence of the acetone bodies and their production in amount sufficient to threaten life is an enormous one. If we speak of a slight production of acids as acidosis, we might say that acidosis is the rule in health, for acids are always being formed in the body and means are always being taken to neutralize and get rid of them; carbon dioxide, a weak acid, is always being given off from the lungs and the kidneys are usually excreting an acid urine. The mere changing of the diet from an ordinary mixed one to one of meat, cereals, bread, butter and prunes, calls upon the defensive mechanism of the body to an extent as great as would the production of several grams of β -oxybutyric acid in the course of 24 hours. This is chiefly due to a change in the mineral constituents of the food. We would hardly be justified in saying that a person on a diet of bread, butter, rice, meat and prunes was suffering from acidosis.

Moreover, it is not the mere presence of the acetone bodies that determines acidosis. In children they are not a very frequent cause. To understand how acidosis may be brought about, or, in other words, how the normal relationship of

*Read before the New York Academy of Medicine, December 2, 1915.

alkalies to acids in the body may be disturbed, it is necessary to consider briefly the method by which the body maintains its equilibrium, in which there is a preponderance of bases over acids.

With extraordinary regularity the blood is maintained at a constant reaction which is slightly alkaline. It is unnecessary to dwell upon the necessity for constancy of reaction further than to remind you of the extreme sensitiveness of the enzyme and chemical actions in the body, which are interfered with or absolutely inhibited by the most minute alterations of reaction in the various fluids. For instance, a change in the reaction of the blood from the normal one to precise neutrality is sufficient to render life impossible. That is, a change from the reaction of ordinary tap-water, which is more alkaline than the blood, to that of distilled water, which is much more acid than blood, would be incompatible with life.

The body is constantly elaborating acids as the result of oxidative processes in intermediary metabolism. For example, sulphuric and phosphoric acids result from the oxidation of the sulphur and phosphorus of proteins, and carbonic acid from the transformation of all organic material. In addition, certain organic acids are formed in small amounts and are usually transformed completely into carbon dioxide and water, although a small quantity of such substances as lactic and uric acids does leave the body unchanged. Also acid radicles predominate in the mineral constituents of many of the common foods. To guard against the deleterious influence of the acids formed in or introduced into the body, a most efficient mechanism is available. It is only necessary to consider here the mechanism from the standpoint of the blood, for this serves to regulate the reaction of the entire body.

The important constituents of the blood, so far as the regulation of the reaction is concerned, are: (a) sodium bicarbonate, occurring both in the plasma and in the cells; (b) the acid and alkaline phosphates of sodium and potassium, found almost entirely within the red blood cells, and (c) the proteins.

Considering the blood first as a solution of sodium bicarbonate: A large amount of acid, carbonic acid, is constantly being formed in the tissues. It must be removed by the lungs, but first it must be transported to the lungs by the blood. This stream of acid which, with an adult, in the course of the day, is the chemical equivalent of several hundred cubic centimeters of concentrated hydrochloric acid, is sufficient to render acid any ordinary solution and keep it permanently acid. If this should happen in the blood, life would, of course, be impossible, but owing to the laws that govern the reaction of solutions of weak acids and their salts, the solutions of sodium bicarbonate are able to take up a quantity of the acid, carbon dioxide, without appreciably undergoing a change in reaction. Thus there can be transported from the tissues to the lungs, and so continuously eliminated from the body, a very large amount of acid. This steady escape of acid is accomplished with no harm and with no strain upon the organism. The respiratory center is adjusted to assist in the removal of the carbon dioxide. If there were no respirations and the circulation were continued, eventually the carbon-dioxide concentra-

tion would be the same in the tissues, in the blood and in the air in the pulmonary alveoli. But the respirations lower the concentration in the lungs and thus allow the carbon dioxide to escape from the tissues where the concentration is highest, by the blood where the concentration is lower, to the air in the lungs where the concentration is lowest. The respiratory center is extraordinarily sensitive to the slightest alteration in the reaction of the blood toward the acid side, so that an increased production of carbon dioxide in the tissues, such as occurs for instance with muscular exercise, and the resultant slight excess in the blood are answered by an increased ventilation of the lungs, which removes the carbon dioxide, thereby bringing the reaction of the blood back to normal. Other acids, whether formed in the body or introduced from outside, produce a similar effect. They displace the carbonic acid from the sodium bicarbonate and set carbon dioxide free. This excess of carbon dioxide is removed by the increased pulmonary ventilation, leaving a neutral salt—sodium β -oxybutyrate or chloride or what not—to be removed by the kidneys. Such a mechanism allows relatively huge amounts of abnormal acids to be at once rendered innocuous and removed. For instance: $\text{NaHCO}_3 + \text{HCl} = \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2$. The hydrochloric acid is neutralized and the resultant sodium chloride is removed by the kidneys, while the carbon dioxide is given off by the lungs.

Henderson¹ calls the carbonates of the blood the first line of defense. Thus, dyspnoea, more properly hyperpnoea or increased pulmonary ventilation, under abnormal circumstances, is an agent of the greatest value in ridding the body of carbon dioxide and thus keeping the reaction within normal limits. It may also be remarked that hyperpnoea is the best of all the evidences of acidosis to be obtained by physical examination alone. It may almost be said that hyperpnoea means acidosis.

If the bicarbonates of the plasma furnished the only method of defense of the body, the organism would succumb to acidosis as soon as the bicarbonate was depleted by the excretion of neutral salts through the kidneys; every molecule of an acid would rob the body of a molecule of bicarbonate. The second mechanism here comes into play and is that by which acids may be removed, leaving behind part of the base with which they have been combined, this base being available for further neutralization. The elimination is by way of the kidneys. These have the capacity to excrete an acid urine from a nearly neutral blood. They remove acid phosphate and save base with each molecule of acid phosphate that they excrete. Thus, although alkali is eliminated in the urine, it is much less than would be the case without this specialized kidney activity and can readily be replaced under normal circumstances by the alkali of the food. For instance, with the introduction of a foreign acid: $\text{Na}_2\text{HPO}_4 + \text{HCl} = \text{NaCl} + \text{NaH}_2\text{PO}_4$. The hydrochloric acid is neutralized, the sodium chloride and acid sodium phosphate are excreted by the kidneys. Or the following reaction may take place: $\text{Na}_2\text{HPO}_4 +$

¹ Henderson, L. J.: Amer. Jour. of Physiol., 1908, XXI, 427.

$\text{H}_2\text{O} + \text{CO}_2 = \text{NaH}_2\text{PO}_4 + \text{NaHCO}_3$. By this method, the sodium bicarbonate reserve of the body is renewed.

Henderson and Adler² showed the magnitude of alkali sparing very prettily by titrating with alkali the acid urine back to the normal reaction of the blood. The alkali spared was found in normal adults to vary, in terms of tenth normal alkali, between 200 and 800 cc. This is equivalent to saying that the kidneys eliminate from 200 to 800 cc. of tenth normal acid in 24 hours.

A third method of defense is afforded by the proteins. The part they play is probably not so great as that of the bicarbonates or phosphates. It depends upon their amphoteric character. Proteins can combine with appreciable amounts of either acids or alkalis without undergoing marked changes in reaction. The details of this action are obscure, but the influence of protein is undoubted. These three means of defense, bicarbonates, phosphates and protein, act synchronously and reside in the blood itself. There are undoubtedly similar measures of defense in the tissue juices and cells of the body.

The body possesses a further means of defense in that it is able to neutralize acid by the production of alkali. The alkali to which we refer is ammonia. In health a small amount of this is always formed and neutralizes an equivalent amount of acid. When acids are introduced into, or formed in, the body in unusual amount, a response occurs in an increased production of ammonia. This is formed at the expense of urea, a neutral substance, and hence represents a clear gain of alkali to the body. The amount of alkali saved to the body in normal subjects approximates that saved by the process of acid-phosphate excretion, but in abnormal conditions, such as diabetes, it may save ten times as much. With such findings it is unnecessary further to emphasize the fact that in ammonia production the body possesses a magnificent means of defense against acids.

From the foregoing, it must be plain that there may be all degrees of acid production and retention. As a result of this it is very difficult to set a limit and say when acidosis is present. There is a range of variation of the temperature in health. Does an elevation of a tenth of a degree above this constitute fever? When can we say that fever begins? It is even more difficult to say when acidosis begins, for the reason that we recognize acidosis largely by the exhibition of increased activity in those defenses that are constantly in operation. Let us, then, consider the means by which it is recognized: We may examine the urine or the blood for the presence of abnormal acids. They may be found and, when found, are evidences of an alteration in the ordinary metabolism; but their mere presence does not indicate that acidosis exists, for they may be entirely compensated for by the various means that have been enumerated, and the functions of the body may be in no wise interfered with on account of their presence. They are in themselves not essentially toxic, and they can prove harmful to the body only by removing bases. In excessive amounts

they are productive of great harm in this way, but this harm can be shown by other methods. Severe and fatal acidosis may, on the other hand, occur when no abnormal acids can be found.

We seek for the evidence of unusual activity of the body's defenses. We determine the amount of ammonia excreted in the urine and its relation to the total nitrogen excretion. This is one of the oldest and most generally employed methods. In many cases of acidosis the ammonia excretion is increased both absolutely and also in relation to the total nitrogen output. A high ammonia coefficient, however, occurs as the result of certain dietetic changes. A high ammonia coefficient always arouses the suspicion of acidosis, but, unless this can be confirmed in some other way, should not be taken as conclusive proof of its presence. On the other hand, fatal acidosis may occur in uræmia and in nutritional disorders of infants with no considerable increase in the ammonia coefficient.

We determine by other means than by mere observation the evidences of increased pulmonary ventilation. This may be done by spirometer measurements, as carried out by Peabody, or by the determination of the carbon-dioxide percentage in the alveolar air. The carbon-dioxide percentage or, more correctly, tension of the blood and of the alveolar air, is the same. The tension is diminished in acidosis.

Why is there a diminished carbon-dioxide tension of the blood in acidosis? For one reason because there is less bicarbonate in the blood. Some of it has been taken to neutralize acids, and what is left is not capable of maintaining the normal reaction of the plasma, when carbon dioxide in the usual amount is poured into it from the tissues. A relative excess of the acid carbon dioxide over the alkaline bicarbonate occurs, with a resulting shifting of the reaction toward the acid side. Thus the respiratory center is stimulated, the increased pulmonary ventilation serves to remove rapidly the carbon dioxide and the carbon-dioxide level in the blood is lowered. The blood reaction tends to return to normal, but as the carbon dioxide is constantly formed, the dyspnea becomes constant unless the sodium bicarbonate content of the plasma is renewed. The quantity of carbon dioxide excreted by the lungs is not appreciably changed, but is diluted as the result of the increased amount of air entering and leaving the lungs. For this reason the carbon-dioxide percentage or tension of the alveolar air is lower than normal.

Bicarbonate deficiency in the plasma is an indication of acidosis. This deficiency may be recognized in a variety of ways. One of the oldest is the determination of the carbon dioxide given off from the plasma when acid is added to it. This method has recently been made applicable to clinical medicine by van Slyke. A diminution in the volume of carbon dioxide given off indicates a depletion of the bicarbonate content of the blood. The test introduced by Sellards³ also indicates a deficiency in bicarbonate in the plasma. It is carried out by removing the proteins of the serum with absolute alcohol and evaporating the filtrate with a few drops of

² Van Slyke: *Proc. Soc. Exp. Bio. & Med.*, 1915, XII, 165.

³ Sellards: *Johns Hopkins Hosp. Bull.*, 1914, XXV, 147.

² Henderson and Adler: *Jour. Biol. Chem.*, 1909, VI, xxxviii.

phenolphthalein. Under normal circumstances a deep purple color results. With acidosis the color is greatly modified or may be entirely absent. Finally the bicarbonate depletion may be roughly determined by giving sodium bicarbonate as recently practiced by Sellards,⁵ Henderson and Palmer.⁶ With acidosis an increased amount is necessary to bring about an altered reaction of the urine. This is usually spoken of as the tolerance to alkalis. The reserve alkali may also be determined by titration of the blood with dilute acid.

We have described the methods by which the body protects itself against acids and maintains the normal reaction of the blood. The defenses may break down. When they do, the reaction of the blood changes. The reaction of the blood may be determined either by the electrical method or by the recently introduced "dialysis-indicator method."⁷ What is determined is the concentration of hydrogen ions. An acid is a substance giving hydrogen ions in solution, an alkali is one giving hydroxyl ions in solution. When the amount of these is equal, the solution is neutral. If the hydrogen ions predominate, it is acid. In any solution both hydrogen and hydroxyl ions are present and their product is a constant. When one increases, the other diminishes. It is thus possible to express the reaction of any solution by stating the concentration of either hydrogen or hydroxyl ions. In uncompensated acidosis the hydrogen ion concentration of the serum is increased. Coincident with this is a diminution in the capacity of the hæmoglobin to combine with oxygen.⁸

The methods that we have ourselves used in the cases to be described have been chiefly the determination of the carbon dioxide in the alveolar air, Sellards' test, the alkali tolerance, the determination of the hydrogen-ion concentration of the serum and the oxygen-combining power of the hæmoglobin, and the quantitative determination of acetone bodies in the blood⁹ and urine.

To consider first the acidosis resulting from the production of abnormal acids: In childhood they are chiefly found in diabetes and in recurrent vomiting. We will not discuss in detail the acidosis of diabetes. It was the earliest recognized, has been the most studied and is the best understood. We have nothing of importance to add to it. But a study of diabetes in children shows very well the enormous amount of acid that may be taken care of with no disturbance of the reaction of the blood and with no effect upon the respiration. Thus, three of our patients, small children, excreted daily in the urine 4.7, 5.5 and 5 gm. of β -oxybutyric acid, respectively. They had also, instead of only a few milligrams of acetone bodies per 100 gms. of blood, as is normally the case, more than 50 milligrams each, a very considerable accumulation of these substances. There was no evidence of acidosis except the presence of these abnormal acids and a high ammonia coefficient.

⁵ *Idem*: *Loc. cit.*

⁶ Henderson and Palmer: *Arch. Int. Med.*, 1913, XII, 153.

⁷ Levy, Rowntree and Marriott: *Arch. Int. Med.*, 1915, XVI, 389.

⁸ Barcroft: *The Respiratory Function of the Blood*, Cambridge, 1914.

⁹ Marriott: *Jour. Biol. Chem.*, 1914, XVIII, 507.

In recurrent or cyclic vomiting the conditions are more obscure. Why should the acetone bodies be produced in excess? It would seem that the explanation is not always the same. Alonzo Taylor¹⁰ has found from the observation of one typical case that the acetone bodies did not appear until two or three days after the onset of the attack, and were then excreted only in moderate amount. The conditions were comparable to starvation and the presence of the acetone bodies might be referred to the starvation. Hilliger¹¹ observed the production of attacks of recurrent vomiting by limiting the carbohydrate intake. When the blood sugar fell to .07 per cent, an attack was precipitated. But we can hardly look upon carbohydrate restriction as the usual cause of attacks of recurrent vomiting, for the majority of attacks occur with children receiving an ample supply of cereals, bread and sugar. Nor are the acetone bodies usually slow in appearing in the urine. They are often found a few hours after the beginning of vomiting. We have determined a large amount in urine voided at seven in the morning, when the initial vomiting had been at two that same morning. Such quantities cannot be accounted for on the basis of starvation.

Recurrent vomiting is a very frequent and equally obscure condition. Why should the acetone bodies be rapidly formed in excess when carbohydrates are given in sufficient amount and when the sugar can apparently be burned? For it does not appear in the urine, nor does it increase in the blood. We have studied a mild and a fatal case. The mild case was perfectly typical and occurred in a five-year-old boy, who had repeatedly had such attacks. He vomited for three days and eliminated in 24 hours 3 gm. of β -oxybutyric acid. His blood sugar was .071 per cent, singularly close to the figures that were found in Hilliger's cases with the onset of the vomiting. There was no evidence of increased activity of his defenses against the acids.

The fatal case was observed only in the last hours of life. A child, 3½ years old, began to vomit without apparent cause and when upon a rational diet. The vomiting was continuous, nothing being retained. His condition rapidly became worse and he was brought to the hospital at the end of 48 hours in coma and with hyperpnœa. Sellards' test showed a great reduction of the bicarbonate of the blood. The hydrogen-ion concentration of the blood was increased. The tolerance for alkalis was increased so much that 9 gm. of bicarbonate of soda given intravenously failed to effect an alteration of the reaction of the urine. A quantitative test for acetone bodies in the blood showed the surprising amount of 170 mgm. per 100 gm., as much as is found in the blood of an adult in diabetic coma. Clearly the acidosis was due to the acetone bodies. The autopsy findings were practically nil.

That acetone-body acidosis may occur without apparent cause in the absence of diabetes is shown by the following case: A boy of three years was sent to the hospital for a tumor of the antrum of Highmore. It was discovered that this was in all

¹⁰ Personal communication.

¹¹ Hilliger: *Jahrb. f. Kinderh.*, 1914, LXXX, 1.

probability secondary to an inoperable tumor of the kidney. There was nothing unusual in his condition, until one evening it was noticed that he was breathing heavily and with a slight effort. The next day hyperpnea was marked. He sat up in bed in much distress. His respirations could be heard at a distance. There was no cyanosis. The bicarbonate of his blood as shown by Sellards' test was much reduced. The reaction of the blood had shifted markedly in the direction of acidity. He was given 7 gm. of bicarbonate of soda intravenously. Before 2 gm. had been injected a distinct improvement in his breathing was noticed, and 20 minutes after the completion of the injection he was breathing quietly and had fallen asleep. An incomplete 24-hour specimen of urine yielded 16 gm. of β -oxybutyric acid and 4 gm. of diacetic acid. Four weeks later the boy, who had been comfortable in the meantime, began again to develop dyspnea. This was brought to a prompt termination by another infusion of bicarbonate.

Our attention has been chiefly directed to a study of the acidosis occurring in the diarrhoeal diseases of infancy. Infants with severe diarrhoea may die with no evidences whatever of acidosis. This is true of the majority. On the other hand, a number of infants with severe diarrhoea do develop evidences of acidosis; and the overwhelming majority of these die. The clinical evidence of the acidosis is hyperpnea.

We began our studies with the suggestion afforded by the hyperpnea and have carried them over two years. Finkelstein¹² has discussed at great length the causation of the symptoms of the picture which he has called "food intoxication." Hyperpnea is one of the symptoms of this. He refers them all to the toxic influence of food products improperly or imperfectly elaborated. His theory is capable of indefinite discussion and argument, chiefly from the clinical side, but lacks a scintilla of definite proof.

It was noticed in 1897 by Czerny¹³ that infants with diarrhoea at times exhibited dyspnea. He called attention to the similarity of their dyspnea to that presented by rabbits poisoned with mineral acids.

It is not always easy to detect hyperpnea in its early stages by observation alone and consequently in a few instances we have found evidences of acidosis by tests when we could not say that hyperpnea undoubtedly was present. But when there has been deep, labored breathing without cyanosis, we have always been able to obtain other proofs of acidosis.

We have found a low carbon-dioxide tension in the alveolar air. So far as we are aware, determinations of the alveolar air of infants have not before been made, owing to the difficulties of collecting the air. We have modified Plesch's¹⁴ method so that it is applicable for use with infants. Whereas the carbon-dioxide tension of the air in normal infants or those without acidosis varies between 35 and 42 mm., in acidosis it is less than this, frequently between 15 and 25 mm. That this is due

to acidosis is strongly indicated by the fact that bicarbonate of soda, given by mouth or intravenously, causes a return of the carbon-dioxide tension to normal or even abnormally high figures and to cessation of the dyspnea. We have found that evaporation of the protein-free serum with phenolphthalein (Sellards' test) is positive with these infants. In beginning acidosis, the color is pink instead of purple; when acidosis is marked, there is no color.

We have found a great tolerance for alkali, so that relatively large amounts of bicarbonate of soda must be administered in order to change the reaction of the urine. We have determined directly the reaction of the blood by the indicator method, and have found in all the severe cases a distinct shifting of the reaction in the direction of acidity. This reaction may again become normal after alkalies have been given in sufficient quantity. And finally, we have obtained evidence of an alteration in the reaction of the blood, by determining a great lowering of the combining power of the haemoglobin for oxygen.

The following case may be taken as representative of several that we have examined: An infant was breast-fed for two months and did well, gaining weight satisfactorily and having no digestive symptoms. He was then weaned and given condensed milk. At the end of one month of this feeding he suddenly became irritable and began to vomit. Four days later diarrhoea began and did not yield to treatment. He was moderately developed and nourished, but showed evidences of recent loss in weight. The skin was loose, hot and very dry. His eyes were deeply sunken and staring; his color grey but not cyanotic. His mouth was dry and his lips parched. His fontanelle was depressed. His respirations were deep, heaving, pauseless, and were accomplished with distinct effort. His heart sounds were of poor quality. His liver was enlarged. He lay usually in a semi-stupor, but when roused was very irritable and cried with a shrill, distressed cry. His white cells were 15,000. His temperature was between 99° and 101° F. His stools were large and consisted only of a brown, watery fluid. The carbon-dioxide tension of his alveolar air was 15 mm., as compared with the normal of 35 mm. The bicarbonate of his blood was much reduced. The reaction of his blood had changed toward acidity and the combining power of the haemoglobin for oxygen was one-fourth that of the normal. The acetone bodies in his blood were not increased. Despite the administration of alkali, by mouth and subcutaneously, he died eight hours after admission to the hospital.

The evidence of acidosis is sufficient. Now what is it that produces this acidosis? Is it the production of abnormal acids such as β -oxybutyric acid? In cases with profuse diarrhoea they have not been found. Occasionally there may be a trace of acetone bodies in the urine, but not a sufficient quantity to account in any way for the symptoms. Keller¹⁵ long ago sought them in vain. They are also not greatly increased in the blood and we have never found more than 25 m.m. per 100 cc. of blood, a smaller quantity than we have found in cases of diarrhoea uncomplicated by acidosis.

¹² Finkelstein: *Jahrb. f. Kinderh.*, 1907, LXV, 1 *et seq.*

¹³ Czerny: *Jahrb. f. Kinderh.*, 1897, XLV, 274.

¹⁴ Plesch: *Zeitschr. f. exper. Path. u. Therap.*, 1909, III, 380.

¹⁵ Keller: *Malzsuppe, eine Nahrung für magendarmkranke Säuglinge*, 1898.

If no abnormal acids are to be found, what other explanation can be offered? Is it due to loss of bases? Keller¹⁸ sought for abnormal acids in an endeavor to account for the high urinary ammonia which is at times present with diarrhoea. In their absence, he had no explanation to offer. Steinitz¹⁹ in 1903, examined the stools in diarrhoea and found an excess of sodium passed by the bowel. A negative sodium balance was thus produced, more being passed in the stools than was ingested in the food. The more recent and much more extensive studies, made at the Babies' Hospital under Dr. Holt's direction,²⁰ confirm the finding of sodium in excess in diarrhoeal stools. Steinitz spoke of his finding as a relative acidosis, believing that alkali was lost to the body and that ammonia was produced to take its place and to neutralize the ordinary acids, such as sulphuric and phosphoric. But in order to prove this, it is necessary to show that potential alkali has been lost or, in other words, alkali capable of neutralizing acid and not merely a neutral salt. For example, an excess of sodium chloride in the stools does not indicate an alkali loss. Uncompleted studies made in our laboratory seem to show that potential alkali is not lost in diarrhoeal stools. At the present time it cannot be maintained that an excess of sodium or potassium in the stools shows acidosis.

In the absence of proof that abnormal acids are present or that base is lost, what further explanation for the production of acidosis can be offered? There is one striking symptom of the severe acidosis of diarrhoea in infancy, and that is a diminution in the output of urine. Complete anuria is by no means unusual. The kidneys are active in removing acid from the body. We have pointed out that the kidneys of the adult eliminate a large amount of acid each day. Suppose that only part of this acid can be eliminated. Some remains in the blood, constantly acting to reduce the alkalinity; for it is constantly being formed. With the knowledge now available this seems a rational explanation, and we are at present engaged in a study of this phase of the question.

Though explanation as to its origin may be entirely lacking, there is no doubt that acidosis occurs in the course of other diseases. It has been suggested by Lewis and Barcroft²¹ that some of the symptoms of pneumonia may be due to acidosis. Two cases that we have observed presented evidence of this complication. A description of one will suffice. A child, two years old, was taken acutely ill with fever and later convulsions. He was admitted to the hospital semi-comatose with the typical breathing of air-hunger, deep, pauseless respirations quite unlike those ordinarily seen in pneumonia. He had consolidation of the left lower lobe. The bicarbonate of his blood was much reduced, and the reaction of his blood had shifted toward the acid side. There was no increase in the acetone bodies. He was infused with sodium bicarbonate solution, with a distinct change in the character of the breathing; but died 54 hours

after the onset of the disease. The pneumonia was caused by Friedländer's bacillus. A second case in a girl of six, also rapidly fatal, was caused by a pneumococcus of the type of *Group 1* of Cole's classification.

Even when no evidence of disease can be detected to which the acidosis can be referred, acidosis may be found. For instance, a boy of six was suddenly taken ill with high fever. Inside of 12 hours he was brought to the hospital with great dyspnoea of the air-hunger type. Physical examination was quite negative except for a purulent otitis media. All the tests made indicated acidosis. The bicarbonate of the blood was greatly reduced. The reaction of the blood had shifted markedly toward acidity and yet the acetone bodies in the blood were not greatly increased. The tolerance for alkalis was enormously increased. Though he took by mouth 20 gm. of soda and 6 gm. by rectum without vomiting or diarrhoea, no change in the reaction of the urine was produced thereby. But the alkalis had a profound influence upon his condition; his respirations diminished in rapidity and depth, the evidences of acidosis to be obtained by the various tests rapidly disappeared and he made an uninterrupted and apparently complete recovery; for he now seems entirely well and has been so for six months.

We may then say that acidosis is not an uncommon condition in infancy and childhood; that while it is especially frequent in the severe diarrhoeas of infancy, it may appear with a variety of diseases, and sometimes, apparently, alone. To recognize it with older children is not very difficult. The character of the respiration is usually sufficient to arrest one's attention and one or two relatively simple laboratory tests will quickly determine the question one way or the other. With infants who are irritable, restless and crying, it is much more difficult to say whether hyperpnoea is present; and yet with them it is most important to make the diagnosis early, for the reason that acidosis is such a fatal complication of diarrhoeal disease in infancy. Older children react promptly and often permanently to alkali therapy. It may be possible to stop the clinical and laboratory evidences of acidosis in infants, but the patients usually die. Why they do cannot be determined at the present time. Many normal processes have undoubtedly been inhibited, perhaps permanently, and many abnormal ones stimulated. A restoration to normal conditions seems nearly impossible. For this reason we should not wait until acidosis can be demonstrated. From the beginning we should give bicarbonate of soda to infants with severe diarrhoea in sufficient quantity to render the urine alkaline and keep it so.

We may lay it down as a general maxim that as hyperpnoea indicates acidosis, so hyperpnoea indicates alkali therapy, and this for infants or older children. The alkalis may be given by mouth, by rectum, subcutaneously or intravenously. Vomiting and diarrhoea frequently render their administration by mouth or by rectum out of the question. Then one of the other methods must be employed. Intravenous administration is the method of choice, especially when rapidity of action is desired—and with acidosis rapidity of action is always desired.

¹⁸ Keller: *Loc. cit.*

¹⁹ Steinitz: *Jahrb. f. Kinderh.*, 1903, LVII, 689.

²⁰ Holt, Courtney and Fales: *Amer. Jour. Dis. Child.*, 1915, IX, 213.

²¹ Lewis and Barcroft: *Quart. Jour. Med.*, 1915, VIII, 97.

The superior longitudinal sinus, as advised by Marfan, Tobler and Helmholtz, is available with infants, or the external jugular or femoral veins. With older children, a vein in the arm can often be employed. If facilities for the intravenous injection of alkali are not at hand, the injection may be made subcutaneously, with care that the bicarbonate has not been transformed into the carbonate, else severe sloughing of the tissues may result. A four-per-cent solution is usually employed for intravenous use and a two-per-cent solution for subcutaneous use. The quantity to be injected depends upon the size of the child, the severity of the symptoms and the effect produced, but the amount is always large. It must be given until the urine becomes alkaline; even in infants under one year, as much as 10 gm. in 24 hours may be required.

With the cases of acetone-body acidosis with no sugar in the urine and with a low sugar content of the blood, glucose

by rectum, subcutaneously or intravenously seems clearly indicated in addition to the alkali. With all forms water is urgently required, especially with infants who are dehydrated as a result of the vomiting and diarrhoea.

Much remains to be learned regarding acidosis. The presence of abnormal acids explains the origin of some forms, but there are others that are in nowise understood. Are there abnormal acids whose presence has not been detected? Are normal acids formed in excess? Are bases lost? Does the kidney fail to excrete sufficient acid? These are a few of the questions at present unanswered that must be answered before our knowledge of acidosis can be considered in any way complete. Much has been learned in the last few years; with the present greatly stimulated interest in the subject, we may confidently expect that the future will provide answers to many of the questions that now seem obscure.

THE USE OF SUCTION IN THE POST-OPERATIVE TREATMENT OF BLADDER CASES.

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My interest in this subject was aroused by a case of extensive carcinoma of the bladder, which could be treated only by fulguration, through a supra-pubic wound. In this patient it was necessary, at the same operation at which the cancer of

able, I attempted to carry off the irrigating fluid by means of continuous suction. The apparatus was arranged as shown in Fig. 1. The sterile water used for the irrigation reached the bladder through a permanent urethral catheter (*a*) which was

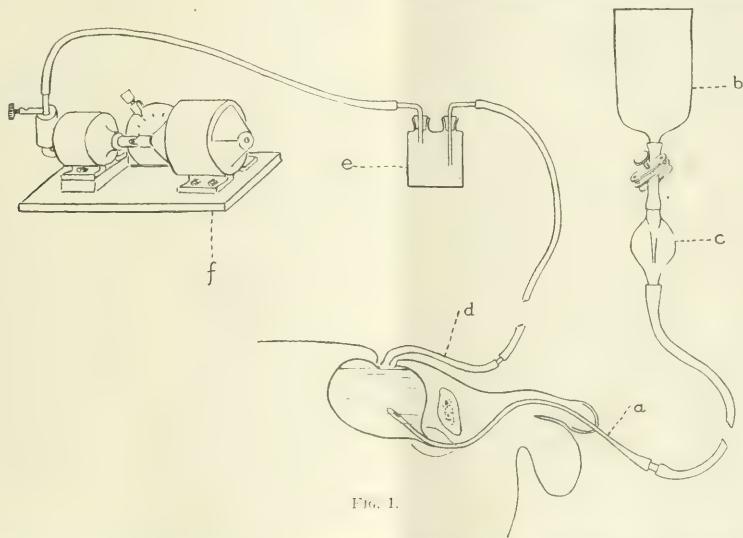


FIG. 1.

the bladder was treated, to do a supra-pubic prostatectomy. In order to rid the bladder of the urinary salts which were deposited on its wall, and to hurry the healing of the supra-pubic wound, it seemed advisable to keep up continuous bladder irrigation; and to keep the patient dry and comfort

connected with a reservoir (*b*) provided with a drip apparatus (*c*). Into the supra-pubic wound a large caliber tube (*d*) was introduced, not deeply enough to enter the bladder itself. This tube was fastened to the abdominal binder and connected with a rotary electric suction pump (*f*), through an air trap

13. This pump is the kind used by Dr. Flint in the post-operative treatment of empyema cases, with satisfactory results as regards rapidity of healing and cleanliness of dressings. With this apparatus it was quite easy to keep a stream of water running through the bladder and out through the operative wound; at the same time the dressings remained perfectly dry, the water being sucked away before it could reach the skin level. The results were an increase in the patient's comfort, a preservation of the skin about the wound, a saving in dressings and an increased rapidity of healing.

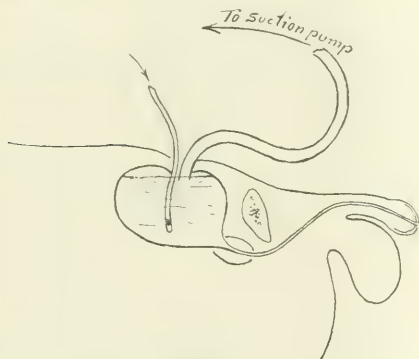


FIG. 2.

The results in this case were so gratifying that a similar arrangement was used in a second supra-pubic cystostomy, save that in this instance both inlet and outlet tubes reached the bladder via the supra-pubic wound and no permanent urethral catheter was used (see Fig. 2).

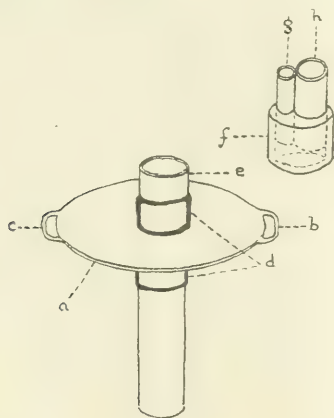


FIG. 3.

The use of combined continuous bladder irrigation and suction in the after-treatment of supra-pubic cases having been thus proved to be of value, the tube shown in Fig. 3 was devised

to facilitate the application of the method. This tube consists of a metal plate (a) provided with two eyes (b and c) through which tapes may be passed to be tied around the waist. The center of the metal plate is pierced by a tube (d), through which a large caliber rubber tube (e)—of such diameter as to fit the metal tube (d) snugly—is passed. A metal cap (f) is made so as to fit snugly over the metal tube (d) in the abdominal plate. This cap is provided with two metal tubes (g and h), the smaller (g) for the insertion of a smaller catheter, and the larger (h) for a moderate-sized drainage tube. The application of this apparatus to a supra-pubic case is shown in Fig. 4. The metal plate (a) has been applied so that

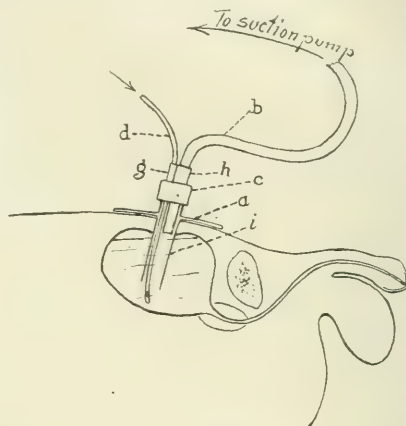


FIG. 4.

the large rubber tube (e) reaches well into the bladder. The cap (f), containing a small catheter (g) (which reaches to the floor of the bladder), and a large tube (h), has been fitted to it. Through the former (d) irrigating fluid is dripping into the bladder, while the excess is being drawn away, before it has had an opportunity to reach the skin level of the abdominal wound, by suction through (b). If either tube (d) or (b) becomes clogged, it may be removed, cleansed, and without any difficulty reinserted through the opening (g) or (h), the supra-pubic wound being held open by the metal plate (a), which has remained in place. If there is still difficulty with the drainage, the cap (c) may be removed, leaving the bladder wound still draining and kept open by the metal plate (a). Through this the bladder may be abundantly flushed, and afterwards the cap (c) with its catheter reappplied; continuous irrigation and suction are then started again.

The value of continuous irrigation, in the cystitis which accompanies hypertrophy of the prostate, has been well demonstrated by Young in his work on the perineal operation; and I have, therefore, attempted to apply it, by the method here described, to supra-pubic prostatectomy. In view of the fact, however, that the post-operative hemorrhage was not diminished, if indeed it was not increased, I have devised the ar-

arrangement shown in Fig. 5 for dealing with these cases. The plate and metal tube (a) are inserted as usual, but the cap with its contained catheters is not applied. Through the tube the gauze packing (b), which is placed down to the bleeding area beneath the prostatic capsule, passes out to the abdominal dressing. At the end of 48 hours this packing is removed. The metal cap is then applied and, the hemorrhage being now controlled, irrigation and suction (as shown in Fig. 4) are instituted.

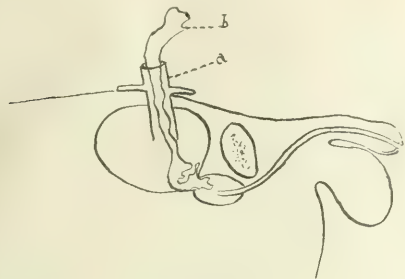


FIG. 5.

In all cases of supra-pubic cystostomy continuous suction (even when continuous irrigation is not used) is of great value in keeping the patient comfortable, saving dressing material and promoting healing; and we are now using the method with much satisfaction as a routine procedure in the New Haven Hospital. If continuous irrigation is not desired, the arrangement is as in Fig. 4, except that the catheter for the in-flow (d) is not used. All that is necessary to keep the accumulating urine sucked away is to have the suction tube (b) below the level of the skin, that is to say, through the abdominal wound. It is not necessary to have air or water-

tight connections or to use strong suction. The large tube (i) keeps the bladder wound open and prevents suction from acting directly on the bladder wall.

The large catheter tube (c), Fig. 3, which fits into the metal tube piercing the plate (d), fits it so snugly as to prevent leakage, but it is not fastened to it and may be gradually withdrawn and shortened as healing progresses. The metal plate and tube are finally removed, and for the last days of healing a suction tube lying just in the wound, as shown in Fig. 1, is sufficient to keep the patient dry. It is to be emphasized that no air-tight or water-tight arrangement is needed; all that is necessary to keep these patients dry is a suction tube the mouth of which lies below the skin level; any fluid which reaches this level is sucked away before it has an opportunity to flow out over the abdomen.

Suction may also prove of value in other sorts of cases, where for purposes of healing it is necessary to keep the bladder empty. I have, for example, recently made this use of the method in a case of bad vesico-vaginal fistula operated on by the supra-pubic route.

With a little ingenuity the principle of continuous irrigation or suction, or a combination of the two, as here described, may be adapted to the particular needs of various sorts of operative bladder cases, and will be found of considerable value. The suction pumps needed are not expensive and one pump may be sufficient for the use of several patients simultaneously. On account of the value of suction in this class of cases, and in thoracic cases, it is planned to provide the newer wards of the New Haven Hospital with a central suction plant. Such a central plant has already been installed in one of the present wards for use in bladder cases, and in empyema cases; and plans are being made to apply a similar system of continuous suction to abdominal cases.

THE RELATION OF ANGIOGENESIS TO OSSIFICATION. BASED UPON THE STUDY OF FIVE CASES OF CALCIFICATION AND OSSIFICATION OF THE OVARY.

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(From the Pathological Laboratory of Beth Israel Hospital.)

The incidence within a short time of five cases of such a rare lesion as calcification and ossification of the ovary, seemed at first a fit opportunity to study the lesion from a morphological viewpoint. A closer study of the specimens, however, revealed so many apparently novel data relating to the finer formation of bone, that inevitably the morphological becomes subsidiary to the histogenetic interest.

CASE REPORTS.

CASE 1. (B. I. H. 2891.)—Ovary removed for "chronic ovaritis." Situated beneath the capsule of the ovary is a corpus luteum that is entering the terminal phase of its evolution. It is still possible to differentiate the outer or lutein cell zone from the central core

of fibrin, although both have undergone nearly complete hyaline degeneration. The outer zone contains a small number of degenerated lutein cells and radiating strands of connective tissue arising from the stroma of the ovary. The fibrinous core is acellular.

Scattered in the outer zone are a large number of focal deposits of lime (Fig. 1). These deposits are small, discrete, roughly spherical and imbedded in a cavity formed by the surrounding hyaline tissue. The core of hyalinized fibrin is free from such deposits.

The remainder of the ovary shows the changes common in the adult ovary.

Summary. An almost healed corpus luteum within an otherwise normal adult ovary; in the outer or lutein-cell zone are scattered discrete deposits of lime.

CASE 2. (B. I. H. 3529.)—S. F., aged 60, was admitted to the hospital October 19, 1912, suffering from chronic nephritis. The patient had been married 30 years, and had had six pregnancies, of which two had ended in abortions. She began to menstruate at 18 years; menopause at 40.

The main symptoms on admission were vertigo, headache, fever and sweating, marked edema of the legs, increasing weakness, cough and expectoration and loss of weight. The urine showed much albumin and many casts. Blood pressure, 200. The patient died in uremia, Nov. 7, 1912.

Autopsy.—Anatomical diagnosis: healed tuberculosis of the lungs; emphysema and congestion of both bases; brown atrophy of the heart muscle with hypertrophy of the left ventricle; chronic congestion of the liver and spleen; chronic interstitial nephritis; "osteoma" of the ovary.

Both ovaries are small and shrunken. In the right ovary, just beneath the capsule, is a mass of ivory hardness, measuring 5 x 3 x 2 mm. The mass is egg-shaped; its surface is convoluted and densely adherent to the surrounding tissue. The mass is surrounded by a narrow zone of dense white tissue resembling in structure and conformation a corpus albicans.

Microscopical Examination.—(Fig. 2). The mass consists of a homogeneous mass of lime embedded within a corpus albicans. The edge is wavy, and sharply circumscribed from the surrounding thin capsule of hyaline connective tissue. With the high power the fine fibrillar structure of the hyaline matrix can be distinguished in the calcareous area. Within the calcareous mass are clefts which are manifestly artefacts, due in all probability to the method of preparation.

Summary.—A homogeneous nodule of lime deposited in a corpus albicans of an atrophic ovary. The lime mass contains no bone or cellular elements whatever.

CASE 3. (B. I. H. 2887.)—R. H., aged 40, married 12 years, no children. Menstruation began at 14, regular every four weeks, and of eight days' duration. For the past few months she has been complaining of severe pain in the lower left abdomen. Pre-operative diagnosis: fibromyomata. Operation by Dr. L. J. Ladinski. Supravaginal pan-hysterectomy.

Gross Description.—Uterus: large fibroid in fundus. Fallopian tubes; both tubes adherent to each other by dense adhesions subtending the posterior aspect of the uterus. The left tube is greatly thickened, straight and spindle-shaped. The lumen is completely obliterated and filled with a fine, white, honeycombed mucosa, which exudes a small quantity of seropurulent fluid. The muscular coat is thickened. At its thickest point, the middle of the tube, it has a thickness of 1.5 cm. The right Fallopian tube is distorted and varies in thickness. At the isthmic junction is a nodule, the size of a bean, typical of so-called "salpingitis nodosa." From this point the tube suddenly becomes narrow for a distance of 3 cm., averaging in diameter a goose-quill, whence it gradually increases in size until at the fimbriated end it is 2 cm. in diameter. The fimbriated end is closed. Section of the tube through the isthmic nodule reveals the typical microscopic appearance of "salpingitis nodosa." In the narrow portion the lumen is very small; there are no villi, and the muscular coats are slightly thickened; at the outer end, the lumen is fairly large, convoluted, and lined with a smooth glistening white membrane. Midway between the lumen and the peritoneal coat, is a thin layer of bone which is continuous around the circumference. This layer is about 2 mm. thick, and its contour conforms to the wavy outline of the tube lumen. The left ovary is greatly enlarged, edematous, and contains numerous fresh and old corpora lutea.

The right ovary is very small, measuring 2.5 x 1.5 x 1 cm., and is deeply scarred. On section a hard dense calcareous mass, 8 x 5 x 4 mm., is found just beneath the capsule. This nodule is situated

within the center of a corpus albicans, being surrounded by a narrow wavy capsule of dense white hyaline tissue. The mass was shelled out with difficulty and was found to be egg-shaped, convoluted like a brain, with shallow sulci. The remaining portion of the ovary shows dense cirrhosis and a large number of corpora albicantia.

Microscopical Examination.—The masses in the uterus reveal a typical fibromyoma with hyaline degeneration.

The description of the microscopic structure of the tube is irrelevant for our purpose and will be reserved for later publication.

Calcareous Mass in the Right Ovary.—The lime is deposited within a corpus albicans, the fine fibrillar structure of which can be seen with the high power shimmering through the lime-containing area. The circumference is very wavy and finely spiculated (Fig. 3). Here and there, manifestly corresponding to the sulci observed grossly, are many bay-like excavations penetrating for short distances into the concretion. These excavations are irregular in shape, vary in size, and with the low power of the microscope appear empty. The surrounding hyaline fibrous tissue, which along the greatest part of the circumference is in close apposition to the lime-containing area, becomes attenuated over these excavations and is gradually lost at the roof of the excavation (Fig. 4). With the high power, however, these excavations contain distinct tissues. *In all these excavations without exception, we find abundant red blood cells, a fine fibrillar network of connective tissue and a few distinct fibroblasts. In some excavations, we can even distinguish a very young blood capillary, formed apparently by a number of fibroblasts arranged circularly. These capillaries contain red blood cells (Fig. 5).* The interior of the calcareous nodule also contains numerous irregular cavities with sharply defined walls, which in general features and size resemble the excavations described above. Indeed a continuity between these cavities and the surface excavations can in many instances be clearly demonstrated. Whether all these cavities communicate with corresponding excavations it is impossible to say, because the study of serial sections was not feasible. As we shall see, the probability that they do is strong. With the low objective, these cavities also appear to be empty. *With the high power, however, the same structures visible within the excavations described above are found here; namely, red blood cells, a fine fibrillar connective tissue, interspersed with fibroblasts, and occasionally very fine capillaries containing red blood cells.*

The remainder of the ovary shows the familiar changes of the hard, cirrhotic, inactive ovary.

Summary.—A patient, aged 40, with fibroids, adherent tubes and cirrhotic ovaries. The right ovary contains a calcareous concretion, the surface of which is deeply excavated, the interior honeycombed with cavities, many of which are demonstrably continuous with the excavations, all of them probably so. These excavations and cavities are occupied by an active tissue, consisting of very young blood vessels, fibrillar connective tissue and fibroblasts, in the meshes of which are many red blood cells.

Epicritical Remarks.—The source of this active tissue cannot be positively demonstrated without serial sections which, because of the unexpected findings, were not made. That this tissue arose from the peripheral blood supply cannot be gained. The sequence of events is probably this: blood sinuses and attendant young fibrous tissue penetrated through the hyaline covering of the concretion from the periphery. In corroboration of this surmise, we find, in the hyaline fibrous capsule, spaces containing the identical tissues described within the excavations and the cavities. When this highly active

tissue making up a blood sinus meets the calcareous concretion, absorption of the lime occurs, resulting in deep excavations into the interior. Coincidentally, the formation of young blood vessels takes place, so that part of the blood is carried within these channels.

We regard these findings and this interpretation as highly significant for the elucidation of the later processes of bone formation in these calcareous concretions, about to be described.

CASE 4. (B. I. H. 2781.)—Rosie L., aged 33, married 9 years; never pregnant. Menstruation began at 14 years; it has been regular, occurring every four weeks and of three days' duration; the flow has been normal. For the past three years she has been complaining of pain in the lower abdomen. Since then menstruation has been irregular and more frequent. It now lasts one week. On examination, there is tenderness in the left fornix. Operation by Dr. L. J. Ladinski; double salpingo-oophorectomy.

Microscopic Description.—Both tubes are covered with remains of old adhesions. The tubes are short, straight and average 1 cm. in thickness. On section, the lumina are large; the mucosa is pale and honeycombed. The coats are thickened. The right ovary is attached by a broad pedicle to the posterior surface of the tube. It is 2.5 cm. long, 2 cm. thick and 1.5 cm. wide. *Microscopic diagnosis of Fallopian tube:* chronic salpingitis. The surface of the ovary is covered with the remains of old adhesions. On palpation a hard mass of bony consistence is demonstrable within the ovary. On removal of the mass, which is effected with difficulty owing to its intimate adherence to surrounding tissues, only a shell of ovary, about 2 mm. thick, remains. The calcareous mass is roughly ovoid and measures 1.7 x 1.3 x 1.1 cm. The surface has a brain-like contour with shallow linear sulci.

Section through the center of this mass shows that it is composed of a shell around a central cavity. The shell is 1.1 cm. thick and of bony texture and consistence. The central cavity is about the size of a pea, has a smooth wall and is filled with a soft fatty-like material resembling sebaceous matter.

Microscopical Examination of the Bony Mass Within the Ovary.—With a very low power, three fairly well defined zones can be made out: (1) an outer zone consisting of lime-containing connective tissue; (2) an inner zone of pure bone surrounding the central cavity; and (3) between 1 and 2 a narrow zone, in which new osseous tissue is in the process of formation. Each will be described in order.

Outer zone. This is rather broad, covering about two-thirds the diameter of the shell and has the same morphology as in Case 3. In other words, it consists of lime imbedded in a matrix of hyaline connective tissue. The edge is wavy, finely spiculated and sharply defined from the encircling coat of hyaline connective tissue. Especially prominent are the same excavations on the surface as were encountered in Case 3 (Fig. 6). The difference is that they are deeper; the fibroblasts are more abundant; the reticular connective tissue is coarser; and, what is especially conspicuous, the blood vessel has a more mature appearance. The vessel is sharply defined, the coat is firmer, and cells of an endothelial type line the lumen. The red blood cells no longer lie enmeshed in the fibrillar connective tissue, but are all contained within the well formed blood vessel. The interior of this zone also contains cavities, which, as in Case 3, correspond precisely in morphology to the superficial excavations. Here, also, communications between the two can be demonstrated. The same description of the excavations just set forth can, therefore, be applied to these cavities. *Inner zone.* This possesses all the histological features of mature bone (Fig. 7). There are bone lamellæ, bone cells, typical Haversian canals lined with a well defined row of osteoblasts. The Haversian canals contain one, sometimes two blood vessels, fibroblasts and a fine fibrillar connective tissue. The bone trabeculæ present irregu-

lar streaky areas, which take the stain of calcification and which may be interpreted as irregular and incomplete areas of lime absorption.

The most significant observation is the exact morphological similarity, except as regards the osteoblasts, to the excavations and cavities in the outer zone. The blood vessels, the fibroblasts and the fibrillar connective tissue correspond in every detail. The presence of the osteoblasts will now be explained. The middle zone. This is rather narrow, but contains within itself all the various stages of new bone formation. The earliest stage is best represented in Figs. 8 and 9. Here we note the same excavations and cavities seen in the outer zone. In addition, however, we note that the periphery of the cavity, instead of being comparatively smooth, has a broken-up, moth-eaten appearance. This change is due to two factors: (1) small, irregular scalloped-like absorptions of lime; (2) a tendency for the fibroblasts to arrange themselves along the periphery of the excavation or cavity in the form of one or more layers of osteoblasts. Distinct transformations of fibroblasts into the round or ovoid cells of the osteoblastic type can be demonstrated. Another change consists of a process of lime absorption in the trabeculæ between the cavities and an abundant deposition of cells within these trabeculæ. The trabeculæ are more translucent. The stain of the underlying hyaline matrix is more prominent. The cells are round or oval with small nuclei and stain rather faintly. It is quite evident, however, that these cells are of the same type as those that lie on the periphery of the cavities and may, therefore, be regarded as having the same origin.

The next step in the process of bone formation is represented in Fig. 10. Here we find the earliest form of Haversian canal. The cavities are like those already described; they contain a well-formed blood vessel, reticular connective tissue, many fibroblasts, and in addition, along the periphery, typical osteoblasts. The walls of these canals are composed partly of the calcareous hyaline matrix interspersed with cells of the osteoblastic type similar to those shown in Fig. 9; and partly of typical bone foci, consisting of lamellæ and bone cells. The bone is sometimes continuous along the greater part of the periphery of the canal; sometimes it is present for short distances in two, three, or more areas of the canal with a calcareous matrix intervening. These bony zones are, as a rule, narrow, sometimes consisting of only two or three lamellæ and, peripherally, sharply defined from the surrounding calcareous matrix. This is especially true of the cavities in the more superficial parts of the middle zone. In the deeper portions the lamellæ are continuous with the osseous tissue of the inner zone.

Fig. 11 represents the last or final stage of ossification and the formation of a fully developed Haversian canal. This stage differs from the preceding only in the fact the canal is lined along its entire circumference with osseous tissue.

In the lower part of the picture we note a small Haversian canal surrounded almost entirely by osseous lamellæ.

It is highly significant for the correct interpretation of the pathogenesis of the new osseous formation, that bone is nowhere found except in immediate relation to cavities or canals. The spaces between the canals are entirely free from bone.

The tissue filling the central cavity contains merely debris and fat.

Summary.—A patient aged 33. Both Fallopian tubes and one ovary were removed for chronic salpingitis with pelvic adhesions. A bony mass is found within the ovary in the center of a corpus albicans. On microscopic section five distinct zones can be demonstrated: (1) a hyaline connective-tissue capsule derived from a corpus albicans; (2) a calcareous zone, in which are bay-like indentations and cavities each containing a blood vessel and active fibrous young tissue; (3) an

ossifying zone, in which the processes of lime absorption, the formation of osteoblasts and osseous lamellæ, and the conversion of the above-mentioned cavities into mature Haversian canals, are manifest; (4) an osseous zone consisting of mature bone, with Haversian canals; (5) a central or so-called marrow cavity showing a smooth wall, containing mostly fat.

Our epicritical remarks will be reserved until after the description of the following case:

CASE 5. (B. I. H. 2883.)—I am indebted to Dr. W. C. Clarke, of Columbia University, for this specimen.

The only facts obtainable are that the mass was about the size of a walnut and was found within an ovary removed from a patient at the General Memorial Hospital, New York City.

Microscopic Examination.—The histology is the counterpart of that in Case 4, the only difference being that the process is more advanced. The three zones, calcareous, ossifying, and osseous, are distinct. The osseous lamellæ are more compact; the blood vessels both in the Haversian canals and in the cortical indentations are sharply circumscribed, possess a firm fibrous wall and are lined with "endothelium." The tissue within the forming and mature Haversian canals presents all the characteristics of fatty marrow; there is abundant fatty connective tissue, firm fibrous tissue and abundant fibroblasts, small round cells and spindle-shaped connective-tissue cells. The majority of the Haversian canals are lined with a distinct row of osteoblasts. Neither in this specimen nor in the preceding are we able to find any osteoclasts.

Summary.—With the exception of the clinical findings, the summary of this case is the same as for the preceding, the only difference being that the ossifying process has manifestly attained a more mature age.

Epicritical Remarks Concerning the Pathogenesis of Ossification in the Ovary.—We deem it a fortunate circumstance that we not only possess five cases of a lesion that is unusually rare, but that each illustrates a stage in the evolution of a process, the details of which have so far been a matter largely of speculation. It can be truly said that there are no gaps in the story that these stages illustrate. By them we are enabled to correctly interpret not only the histogenesis of so-called "osteomata" of the ovary, but also of the majority of abnormal ossifications occurring within the human frame.

Briefly, the process is the following. In the apparently dying or inert tissue of the corpus albicans, there occurs a discrete deposit of lime. This is illustrated in Case 1 (Fig. 1). By coalescence these discrete deposits form a solid amorphous calcareous mass within the center of the corpus albicans, the surface of which corresponds in a rough way to the shape of these structures. This is illustrated in Case 2 (Fig. 2). The deposition of the lime does not occur homogeneously, but within the hyaline connective tissue of the matrix of the corpus albicans as a base. In other words, should the lime be dissolved, a cavity within the corpus albicans is not formed thereby, but the underlying hyaline connective-tissue matrix will persist.

Owing to a stimulus, the nature of which is not determinable, ovarian blood vessels arising from the capsule of the corpus luteum penetrate the hyaline connective-tissue membrane and, as they approach the calcareous nodule, are transformed into blood sinuses consisting of a reticulum of delicate connective

tissue and young fibroblasts, both derived from the attendant connective-tissue coat of the penetrating blood vessel. These sinuses erode the surface of the calcareous nodule and, penetrating the interior, form an inter-communicating system of cavities or canals. Some of the fibroblasts arrange themselves circularly and form a very young blood vessel, which eventually carries much of the blood that has hitherto permeated the surrounding loose fibrillar connective tissue. The canals thus formed represent the earliest stages of the Haversian canals. All these steps are nicely illustrated in Case 3 (Fig. 4). The fibroblasts now assume the function of osteoblasts. From irregular delicately appearing cells with a large faintly staining nucleus, they become larger, oval or round, with a strongly defined nucleus, richer in chromatin. These cells tend to arrange themselves along the periphery of the canals and even penetrate into the surrounding areas, in which there has coincidentally occurred an absorption of lime. At the same time, the blood vessel of the canal has matured and now consists of a well circumscribed wall of fibroblasts and fibrous connective tissue. The blood vessel now contains all the circulating blood cells, none being demonstrable in the surrounding connective-tissue meshes. The surrounding reticular connective tissue is harder in appearance, the strands being thicker, denser and interspersed with spindle cells derived from fibroblasts (Figs. 6, 7, 8 and 9).

A deposition of bone now occurs along the wall of these canals; the underlying hyaline calcareous matrix becoming converted into osseous lamellæ, the osteoblasts becoming converted into bone cells. The ossification begins at one or more areas of the wall, until finally the entire canal becomes surrounded by osseous lamellæ (Figs. 10 and 11). The ossification proceeds eccentrically, beginning in the central portions of the calcareous mass and extending peripherally. The bone lamellæ are also deposited eccentrically in relation to the individual cavities themselves, the layers becoming more numerous until they meet the lamellæ of the neighboring canal. Coincidentally with this process of ossification, the contents of the canals mature progressively. The blood vessel enlarges, the fibrous tissue wall is thicker and denser and a distinct endothelial lining is visible. The surrounding reticular connective tissue is also firmer, denser, abundantly interspersed with spindle cells, and has in part become occupied by fatty connective tissue. A distinct layer of osteoblasts now lines these canals. In other words we now find an intercommunicating system of Haversian canals surrounded by osseous tissue, the whole conforming in every detail to normal calcareous adult bone.

The process is entirely analogous to the physiological endochondral ossification, the difference being that, instead of cartilage, the matrix is hyaline connective tissue infiltrated with lime. A description of endochondral ossification taken from Stöhr will show how striking this analogy is. "The first indications of this process consist in changes at certain places within the cartilage; a deposition of lime salts takes place within the matrix, in consequence of which it becomes finely granular and dull: it calcifies. Such places can soon be recog-

mized by the unaided eye, and are called centers of ossification, better perhaps, centers of calcification. Meanwhile, on the surface of the center of calcification, a tissue rich in blood vessels and young cells, the osteoblastic tissue, has made its appearance. This penetrates into the cartilage, and causes the destruction of the calcified matrix; the cartilage cells are set free and disintegrate. In this way a little excavation arises in the center of calcification; it is called the primary marrow cavity.

"These processes are repeated in the immediately surrounding cartilage; that is, the cartilage ground-substance calcifies, the cartilage cells enlarge, new portions of the cartilage break down, and as a result the primary marrow space is gradually and continuously enlarged. At the same time the capsules of many cartilage cells are opened, the cells degenerate, and the intervening calcified matrix projects into the marrow space in the form of irregular processes. The marrow cavity is now a bay-like space, filled with blood vessels and primary bone-marrow, that is, with anastomosing branched connective-tissue cells. Some of these cells, the osteoblasts, grow rich in protoplasm and apply themselves in the manner of a endothelial epithelium to the walls of the marrow cavity and there produce bone. Some of the branched connective-tissue cells retain their form and later, together with a fine-fibered connective-tissue, contribute the supporting framework of the bone-marrow. Others of these cells become fat cells. Through the activity of the osteoblasts the marrow cavity is soon clothed with a thin stratum of bone, gradually increasing in thickness; the irregular processes of calcified substance are completely enveloped in young bone. Thus, step by step, the former solid piece of cartilage is transformed into spongy bone, the trabeculae of which still contain residues of cartilage matrix."

The analogy between the pathogenesis of abnormal ossification and endochondral ossification is admitted by many observers. (Wells,⁴ Buerger and Oppenheimer,⁵ Mönckberg,⁶ Ruh,⁷ Kaufmann,⁸ and Aschoff.⁹) All are agreed that the matrix for subsequent ossification is a calcified area.

Relation between Calcification and Ossification.—Calcification is a common pathological phenomenon and has been described as occurring in almost every tissue of the body. In the instances in which the process has been carefully studied, it has been found that it only occurs in areas of tissue that are dead or inert. For instance, we have observed it in tubercles, atheromatous plaques upon the lining of the circulatory system, a necrosed epithelioma of the abdominal wall, the walls of degenerated sebaceous cysts, and in the wall of an old lung abscess. On the other hand, calcification possesses a peculiar predilection for connective-tissue structures that have undergone hyaline degeneration, which, owing to their complete loss of blood vessels, can justly be regarded as inert tissues; our corpora albicantia may be cited as examples. In addition, we have observed instances of calcification in the hyaline wall of a chronically inflamed Fallopian tube, in the wall of a hernial sac of long standing, in old pleuritic thickenings, in the walls of old hydatid cysts, in old fibroids of the uterus, in the wall of a degenerated ovarian cyst and in the scar of a laparotomy

wound. Indeed, this phenomenon has been observed in almost every instance when hyaline degeneration of a connective-tissue structure may occur.

The chemical process whereby lime is deposited in tissue affords an interesting and fruitful study, but is not germane to our present purpose. For an able discussion of the modern aspects of this theme, the reader is referred to the paper by Wells.

Thus far, every instance of abnormal ossification, exclusive of that directly associated with bony structures, *e. g.*, exostoses, has revealed a coexisting calcification. In no instance, furthermore, has the writer been able to discover a case of unalloyed ossification. Inasmuch as all observers agree that calcification always precedes ossification, both normal and abnormal, the postulate may be formulated that *without calcification there is no ossification*. From this postulate, we may conclude that ossification may occur in any situation where calcification has been observed. A study of recorded cases proves that this deduction is correct, so that a typographical list of abnormal ossifications becomes merely a duplicate of that of abnormal calcifications. We are not in the position to state (because in the present state of our knowledge it is obviously impossible to determine precisely) that the process of calcification ceases when that of ossification begins. In all probability, however, deposition of lime occurred on the periphery of our mass, coincidently with the ossification arising within the center. We deduce this surmise, because we have never observed, or seen reported, a case of pathological ossification within the soft tissues (independent of the bony framework) without a coexisting area of calcification.

THE RELATION OF THE DEVELOPMENT OF NEW BLOOD VESSELS TO THE PROCESS OF OSSIFICATION.

The succession of events comprising the process of ossification, as we conceive it, agrees in its broader features with the conventional view. Our own contribution to the subject is an attempt to resolve the process to its ultimate cellular beginnings; to show how the development of new blood vessels is the essential activity in the making of bone. This activity applies not only to the making of abnormal bone, but also (and this is of vaster consequence) to the making of normal bone. To be sure, in the conventional view concerning the development of bone the important rôle that blood vessels play is well recognized. Their mere presence is accepted as an axiom, their main function being to erode the calcified ground substance so as to form Haversian canals. As we have shown, however, it is not the presence, but the development of these vessels that supplies the keynote of the process of ossification; furthermore, we have shown that the cellular elements that enter into the process of this development are the progenitors of all the histological components of osseous tissue.

The validity of this contention obviously depends upon the soundness of our exposition of the development of blood vessels. We confess that, at the outset, we felt considerable hesitancy in accepting the interpretation of the histological findings in our specimens, inasmuch as they were entirely inconsistent with

the view that we had previously been taught. Never having hitherto made an intensive study of the developments of blood vessels, we were unaware, for a time, that a conception similar to our own had already been published. By a strange coincidence, we were soon put into a close and personal touch with such studies. The result has been that whatever hesitancy we felt at first has disappeared, and we have come to the definite conclusion that the conception, independently worked out by us, is the correct one. This inevitably leads to a discussion of angiogenesis, a subject that has been the source of much controversy.

Theories Concerning Angiogenesis.—The older view* was first advocated by His and until recently was accepted by most histologists.

In this conception, blood vessels originate as protoplasmic cords arising from the terminal portion of a previously existing blood vessel. These protoplasmic cords were termed by Brenner *angioblasts*, and consisted of cellular processes derived from the endothelium of the blood vessel. By the simple process of canalization, these angioblasts become capillaries, the potential element of all blood vessels.

This conception necessarily deduces a postulate of tremendous import to cellular ontogeny, the specificity of endothelium. This has been forcibly summarized by Rabl in his dictum "Endothel stammt aus Endothel." The importance of proving whether the endothelial cell is, or is not, specific is obvious. If endothelium is specific, its functional range, both normal and pathological, at one stroke becomes a very limited one. As Schulte⁷ admirably expresses it: "The doctrine of the specificity of endothelium takes endothelium out of the series of mesenchymal derivatives and separates it absolutely from the blood, should that prove to be of mesodermal origin. Consequently thinkers who support this view have seen the importance of assigning an endodermal origin to both blood and endothelium. Could this be established, it would lend a degree of antecedent probability to the doctrine of the angioblasts, but strictly speaking, it is not a necessary postulate, for a tissue arising diffusely from the mesenchyme, as development proceeds, may be confined to definite localities or even ultimately be restricted to homoplastic proliferation. Such a tissue would be specific if it yielded no heterogeneous products, and I feel myself that this latter property enters more largely into an idea of specificity as applied to tissues than the continuity or origin of their elements. It would seem, therefore, that the advocates of specificity have charged themselves rather to prove that endothelium, once formed, produces only endothelium and never any other elements, for example, blood and connective tissue, than that it is peculiar in its origin."

The modern theory of angiogenesis, first proposed by Rückert and Mollier,⁸ since then warmly advocated by Huntington,⁹ Schulte, McWhorter and Whipple,¹⁰ McWhorter and Miller,¹¹ and Hahn,¹² assumes that blood vessels consist of clefts

or spaces within the mesenchyme bounded by the indifferent mesenchyme cells. The clefts or spaces enlarge and fuse together to form blood vessels, while the lining mesenchyme cells flatten and form "endothelium." This theory has been termed the "adaptive" theory as apposed to the "specific," and predicates the postulate that the endothelial cell is a derivative from the widely distributed mesenchyme cell. To quote Schulte again: "This view thus extends the period of development, and enlarges the area in which it is active to practically the whole body of the embryo. It does not deny that endothelial cells undergo mitosis, that vessels after formation lengthen, or that they may branch and send out sprouts, for it by no means implies that endothelium does not grow, but it relegates the phenomena dependent upon endothelial cells to a later period in the life of the embryo."

This is not the place, nor indeed are we in the position, to adjudicate the arguments of the contending exponents. We have contented ourselves with merely stating the opposing views and indicating their possibilities. The data relating to this subject are immense and have been admirably criticized by Schulte, to whose monograph the reader is referred. As Schulte shows, the divergence in viewpoint is due rather to methods of interpretation than to differences in method and technique. Certainly the observations and arguments of the advocates of the adaptive theory are more convincing than those of their opponents. The recent work of McWhorter and Miller,¹¹ and of Hahn,¹² who showed by delicate operations upon the embryo that blood vessels formed in the area pellucida even when the angioblastic anlage in the area opaca was cut off, affords to our mind irrefutable evidence that the adaptive theory is the correct one.

However, whatever may be said as to the merits of the contending views, the fact that we independently deduced the mesenchymal origin of blood vessels from the histological study of our specimens of calcification and ossification of the ovaries leaves us no choice in the position we shall take. It may seem hazardous to transfer a conception of the development of blood vessels from the domain of the normal to the pathological, but the work of W. C. Clarke,¹³ who showed that the adaptive theory of angiogenesis applies as well to the development of blood vessels in granulative tissue, eradicates whatever misgivings we may have had on this score.

The important rôle that blood vessels play in the process of ossification consists essentially in bringing into heteroplastic activity a dead or inert tissue. In the instances which we report, the tissue is hyaline connective tissue impregnated with lime salts. How is this activity brought about?

Curiously, the most obvious function of blood vessels, namely, the carrying of nutriment, is only subsidiary in the process of ossification. The main function lies in the production of new connective tissue engendered in the process of development of the blood vessels themselves. As we have demonstrated in Fig. 5, this tissue consists of two elements: (1) young fibroblasts; (2) a fine fibrillar intercellular substance. This is obviously a derivative of the fibroblasts, and its origin, therefore, need concern us no longer. The origin of the

* For the best summary of this view see Minot, Kraus and Sabin, in Keibel and Mall's "Handbuch der Entwicklungsgeschichte der Menschen," Leipzig, 1912.



FIG. 2 (Case 2).—Calcareous concretion within the center of a corpus albicans of the ovary.

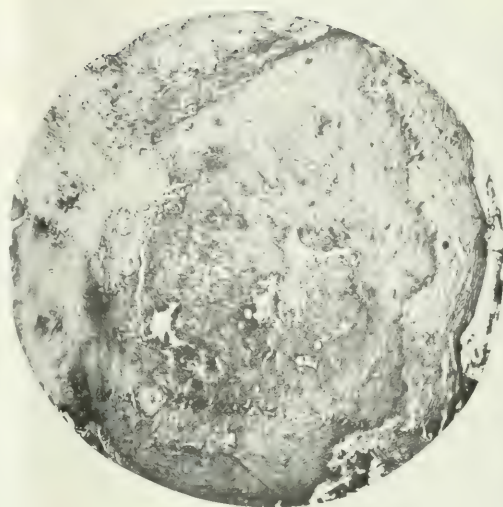


FIG. 3 (Case 3).—Low-power section of a calcareous nodule within a corpus albicans of the ovary. Below is the hyaline connective-tissue capsule. Next to this the spiculated edge of the calcareous nodule. Within, the connective-tissue stroma infiltrated with lime, and containing spaces filled with fibrillar connective tissue, fibroblasts and red cells.

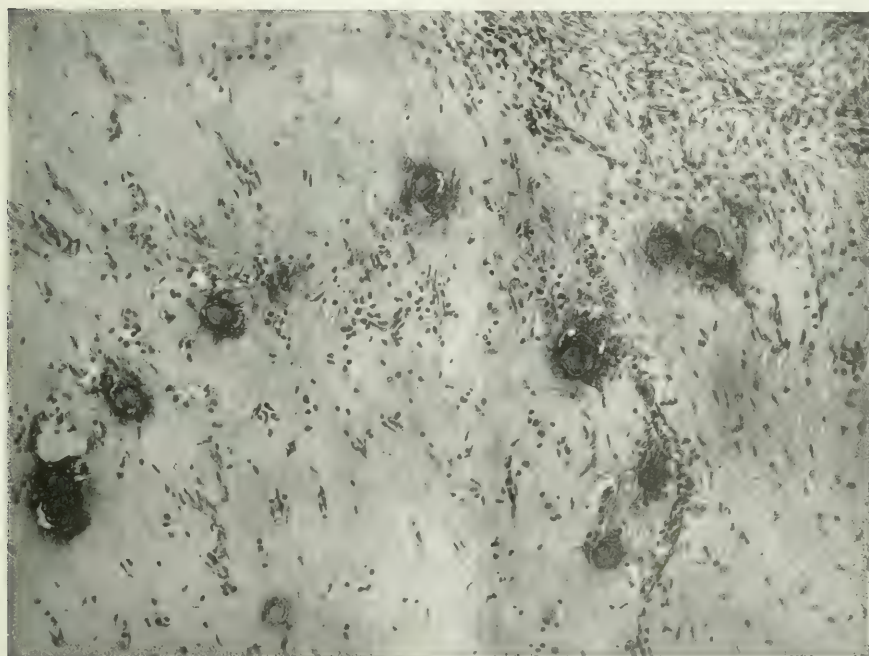


FIG. 1 (Case 1).—Healing corpus luteum of the ovary showing discrete deposits of lime in the yellow zone.

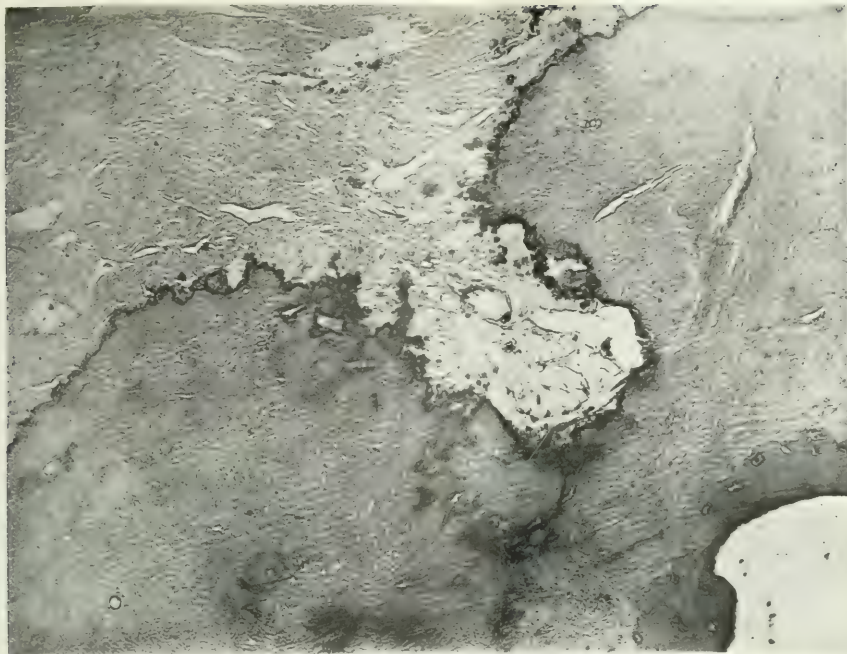


FIG. 6 (Case 1). High-power microphotograph, showing the indentations and cavities within the lime-containing area. These contain a blood vessel, fibrillar connective tissue, and a few fibroblasts. All these structures are more mature than in Fig. 5.



FIG. 4 (Case 2). Primitive Haversian canals (low power). Excavations and cavities within the calcareous nodule. These contain a fine fibrillar connective tissue, a few fibroblasts, and many red cells. These structures are very faint (staining poorly, owing to the decalcifying solution), and therefore do not photograph well.

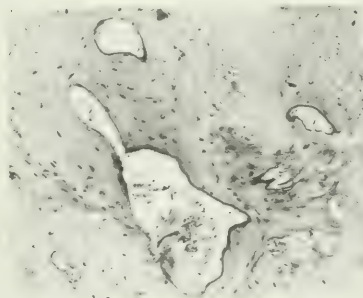


FIG. 11 (Case 5). Numerous Haversian canals, each surrounded in whole or in part by bone lamellae, lime-containing hyaline connective tissue intervening.



FIG. 5. High-power sketch of the preceding (Fig. 4).

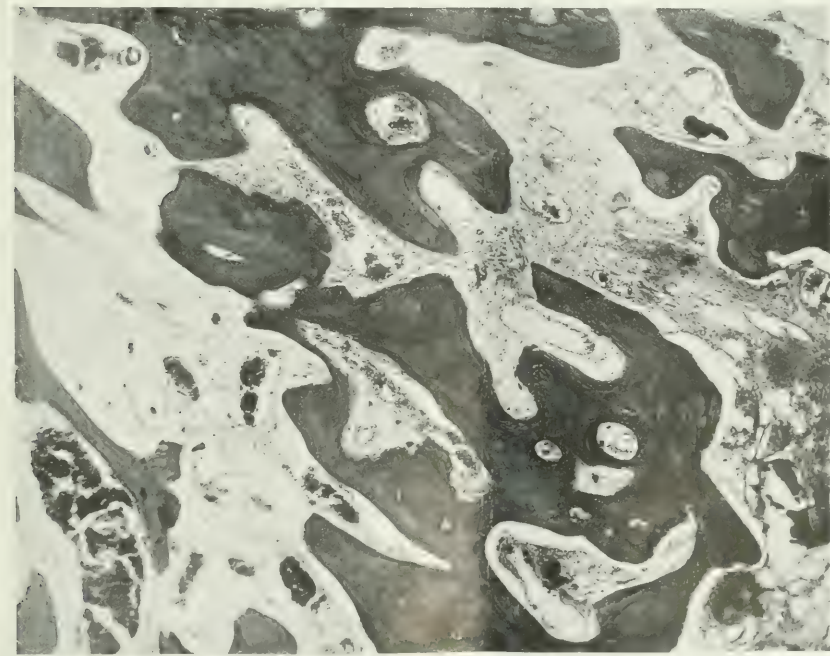


FIG. 7 (Case 1). From the interior of a bony nodule within the ovary, showing bone lamellae, Haversian canals and bone marrow.

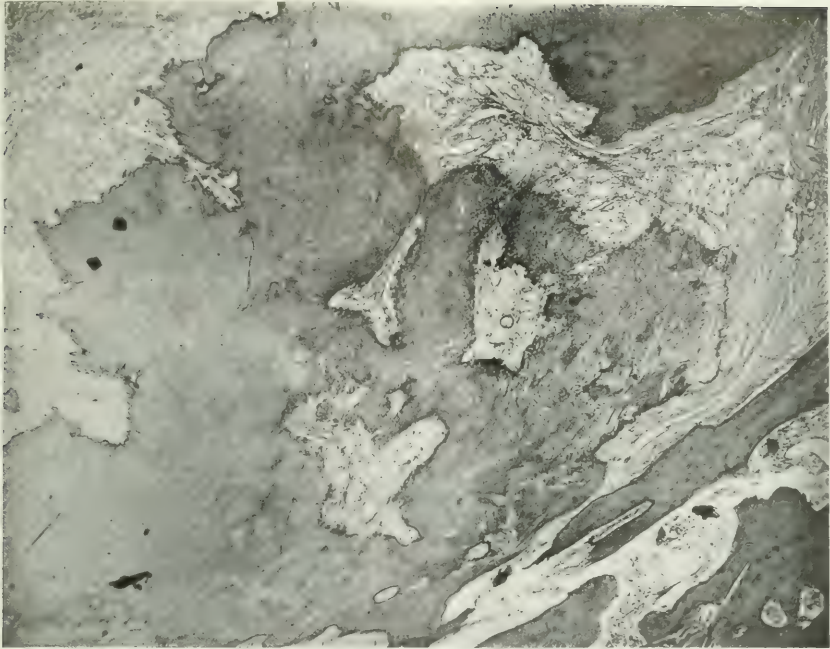


FIG. 8 (Case 4). Low-power section taken near the periphery of the bony nodule. Shows space within the line-containing area filled with delicate fibrous tissue, fibroblasts and young blood vessels. Along the circumference of these spaces are fibroblasts which have penetrated into the surrounding line-containing tissue, which reveals a coincident lime-absorption.

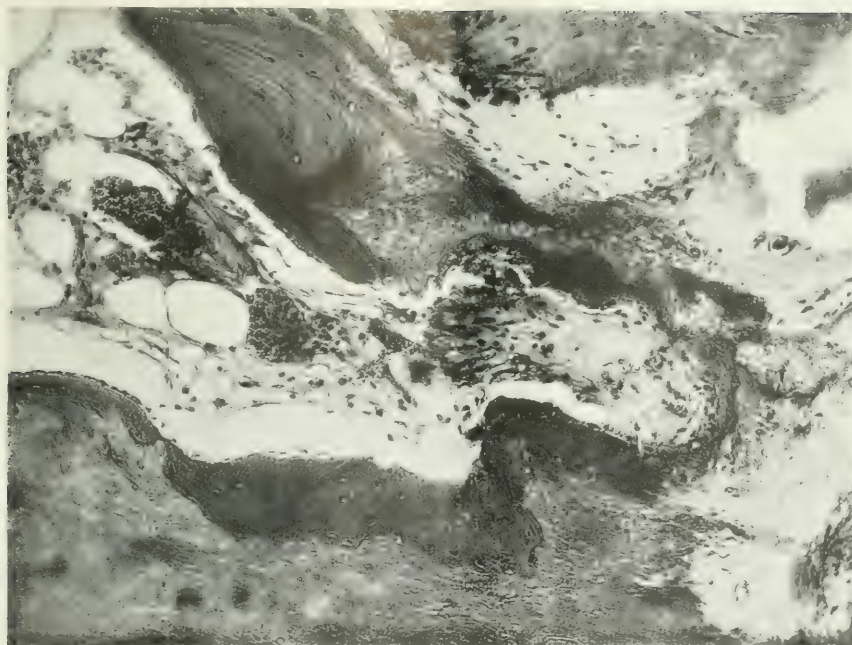


FIG. 10 (CASE 5). High-power; shows an Iversian canal surrounded by a narrow zone of bone lamellae.

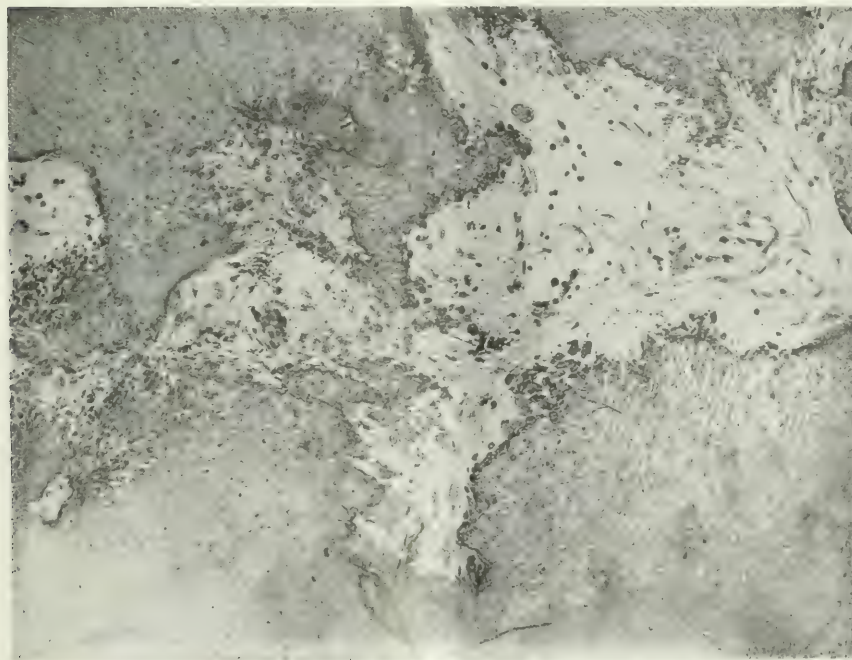


FIG. 9 (CASE 4). High-power of Fig. 8.

fibroblasts is not so easily settled. In ossification of the ovary, these fibroblasts can have only two sources of origin: (a) the endothelium; and (b) the connective-tissue wall of the penetrating blood vessel. Inasmuch as we have shown that fibroblasts later become endothelium, the presumption is strong that the process in its earlier phases is reversed and that, therefore, these fibroblasts are, entirely or in large part, derivatives of the vascular endothelium of the penetrating blood vessel. In embryos, as Huntington, Schulte and others have shown, and in granulative tissue, as W. C. Clarke has demonstrated, these fibroblasts arise not only from the endothelium of the preformed vessel, but also, but in a smaller measure, from the fixed connective-tissue cell. As the hyaline connective tissue in which the lime is impregnated contains no fixed connective-tissue cells whatever, in our series this origin can be excluded.

However, the problem of the exact origin of these fibroblasts is of academic interest. For our purposes, their ultimate fate is a greater issue. As we have shown in our series, the fibroblasts assume three different functions: (1) as vascular endothelium; (2) as osteoblasts; (3) as constituents of the bone-marrow of the subsequent Haversian canals.

In the genesis of ossification their functions as osteoblasts is manifestly the most important.

A study of Figs. 3 to 8 can leave no doubt of the origin of osteoblasts from fibroblasts. In every physical property they are identical with the fibroblasts in their immediate vicinity. Here we note another instance of the close analogy between normal and abnormal ossification, for in developing bone the same origin of osteoblasts is accepted (Stöhr).

The exact manner whereby osteoblasts succeed in converting a calcified hyaline matrix into bone-plates is a matter entirely of speculation. Certainly histological data furnish no clue. In all probability, the influence is a physico-chemical one, a process covered with indifferent satisfaction by the term "metaplasia." Speaking in terms of histology, the process may be described as the following. Osteoblasts are arranged along the edge of the subsequent Haversian canal, which at this stage is bounded by a wall consisting of a calcified matrix of hyaline connective tissue. These osteoblasts penetrate for a greater or lesser distance into the lime-containing area (Fig. 9). The areas where osteoblasts are found stain much lighter than other areas, indicating a coincident lime absorption. Whether this absorption is due to activity of the osteoblasts or to a chemical action of the juices brought by the newly formed blood vessels, cannot be determined. At all events, soon after the penetration of the osteoblasts, bone-plates are deposited around the circumference of the future Haversian canal. This deposition is eccentric. As the bone-plates form, the osteoblast is converted into a bone cell.

The only detail in the histological picture that now calls for elucidation is the further development of the Haversian canal. As we have seen in Figs. 2 and 3, these are first represented by cavities or indentations on the surface of the lime-containing area, filled with a fine fibrillar connective tissue, fibroblasts and a blood sinus. In the next stage (Fig. 4), the blood sinus becomes a frank blood vessel with an endothelial wall. The

fibroblasts are more abundant and the fibrillar connective tissue is coarser. The subsequent changes (Figs. 5, 6 and 7) show a gradual senescence of these elements. The blood vessel is accurately shaped and is composed of a firm connective-tissue wall with a distinct lining of flattened endothelial cells. The fibrillar connective tissue is coarser, the fibroblasts are more abundant, the cell bodies and nuclei are more precise in outline, and the chromatin network is richer. The osteoblastic arrangement of the cells is more pronounced. Finally (Fig. 8), we have the mature Haversian canals with all their elements attaining their fullest fruition. In addition, we find that some of the connective tissue has undergone fatty change, and we find abundant round cells of the lymphoid type. In other words, the resemblance to the normal Haversian canal of normal bone is now complete.

A curious feature of ossification is the eccentricity of the process, the reverse of what we should expect from the concentric mode of development of the new blood vessels. This phenomenon is the counterpart of that occurring in the development of normal bone, in which we find the ossification proceeding from "centers."

Nature of Ossifying Stimulus.—There still remains the question as to the nature of the stimulus that converts a calcified tissue into bone. We must presume there is a stimulus, because not all foci of calcification turn into bone. It is nevertheless still debatable whether ossification is not an invariable consequence of calcification, given a sufficient period of time. Certainly pathological data indicate that ossification is the rule rather than the exception. For instance, Poscharisky¹⁴ found bone in all but four of 29 cases of calcification of the eye. Of 28 calcified nodules in the lung, 17 contained bone.

Lick¹⁵ produced bone experimentally in the pelvis of the rabbit's kidney as early as 16 to 20 days after ligating the artery, provided that the kidney was wrapped in omentum to secure a free collateral circulation. Without the collateral circulation, the process required three months. With too free a circulation, therefore, there occurs no calcification or ossification; with too little, necrosis occurs, followed by slow calcification, and either a late or no ossification. Apparently, therefore, a fine adjustment of blood supply is an important factor in abnormal bone production.

Wells believes that the stimulus is probably a tactile one, due to the presence of calcium salts. This is supported by the experiments of Barth,¹⁶ who healed bone defects by introducing lime or dead bone, whereas, on the other hand, ossification was not stimulated by the introduction of decalcified bone.

The stimulus is undoubtedly a physico-chemical one, but the precise circumstances suggest an interesting field for future study.

SUMMARY.

4. Three cases of calcification and two of ossification of the ovary are described. The process in each instance involved a corpus albicans. The specimens represent an apparently continuous series, in which four stages are recognizable: (1) an early discrete multiple deposit within a healed corpus luteum; (2) a definitely circumscribed deposit of amorphous lime

within a corpus albicans; (3) the formation of primary Haversian canals—which is accomplished by the genesis of an active mesoblastic tissue, both upon the surface and within the interior of such a circumscribed lime deposit. This mesoblastic tissue is derived from the adjacent blood vessels of the ovary, and the predominant activity is the development of new blood vessels. Associated with this activity is the development of osteoblasts from the mesenchymal cells; (4) true bone formation—with maturation of all the elements described above, together with eccentric deposition of bone-plates around the primary Haversian canals and the formation of marrow.

B. The development of new blood vessels affords the keynote to the interpretation, in terms of cellular ontogeny, of the process of ossification. The histological constituents which enter into the formation of new blood vessels are the progenitors of all the histological components of osseous tissue. In other words, blood vessels, osteoblasts, bone cells and marrow (in large part at least) are merely differentiations of the mesenchymal cell unit.

C. Our specimens furnish strong corroboration of the "adaptive" or "mesenchymal" theory of angiogenesis, and to the theory of the non-specificity of endothelium.

D. Ossification does not occur without preliminary calcification, and calcification occurs only in dead tissues.

E. There is no valid reason for regarding bony structures within the ovary as blastomata.

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THE PRESSURE OF BILE SECRETION DURING CHRONIC OBSTRUCTION OF THE COMMON BILE-DUCT.*

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It is frequently observed in animals with experimental obstruction of the common bile-duct that a rupture of the bile passages may occur with escape of bile into the peritoneal cavity. The following experiments were undertaken to ascertain whether, following an obstruction, there is a rise in pressure within the bile passages from day to day.

A paper by Herring and Simpson¹ gives figures for the dog, cat, rabbit, and monkey. The animals were all put under the influence of an anæsthetic and the experiments lasted but a few hours at the most. The pressure in millimeters of bile varied in cats from 210 to 375, with a mean of 304.4; in dogs from 243 to 342, with a mean of 300. These observers found that stimulation of the vagi caused a somewhat prompt fall in bile pressure. Our experiments show no constant reaction following vagus stimulation, and it is possible that the explanation of this difference lies in the duration of the obstruction.

METHOD.

The animals were anæsthetized with ether. Under aseptic conditions the common duct was ligated with silk thread as

near the duodenum as possible. In two cats the duct was cut. The animals were allowed to recover from the operation, and were given food and water. At the time the pressure was to be recorded they were again put under ether. A glass cannula was inserted into the common duct, which was clamped above this point. A vertical glass tube containing a solution of 1/10 of 1 per cent sodium carbonate or sodium hydrate was connected with the cannula by means of a rubber tube. The fluid in the glass tube was adjusted to the probable pressure level and marked. The clamp was then loosened very slightly to give a slight rise or fall, and the tube raised or lowered to meet it. Final adjustment with the meniscus at the mark on the glass tube having been easily made in this way, the glass tube was fixed in a burette stand, the clamp was completely removed from the common duct, and readings were made at frequent intervals during the experiment. The pressure was determined in millimeters, the measurement being made between the top of the fluid column and the level of the junction of the common duct cannula. The abdominal wound was then closed tight, but the anæsthetic was continued to the end of the experiment, when the animal was sacrificed before it had recovered consciousness.

The pressure was taken in 12 cats, and ranged from a minimum of 236 to a maximum of 360, with a mean pressure of 278 mm. The pressure remained remarkably constant, not

*This paper was completed during the year 1913-1914, but publication was delayed because of its transportation to the Pacific Coast. [G. H. W.]

¹Herring and Simpson: Proc. Roy. Soc. London, 1907, LXXIX, 517.

rising or falling more than a few millimeters during several hours. The column of fluid usually rose and fell a millimeter with respiration, but in the case of the cat giving the highest pressure it varied 5 mm. with breathing.

We obtained no uniform variation in bile pressure by the stimulation of nerves. Electrical stimulation of the right vagus gave an increase in pressure in five animals with a maximum of 5 mm. The stimulation of the left vagus caused a rise in two and a fall in one of 1 mm. When the column of fluid was reduced to one-half, stimulation of either vagus caused sometimes a rise, sometimes a fall. The maximal change was a rise of 33 mm. with stimulation of the right vagus. The maximal fall was 3 mm., also caused by stimulation of the right vagus in another cat.

TABLE I.

Cat No.	Weight in lbs.	Days after operation.	Bile pressure in millimeters.	Dog No.	Weight in lbs.	Days after operation.	Bile pressure in millimeters.
2	...	2	244	1	15	2	278
5	7	2	284	2	17	2	292
7	7.5	2	257
14	8	2	* 292
15	8	2	† 270
3	...	3	297
9	7.8	3	290
13	7.3	3	267
10	11.8	5	236
12	6	5	360
8	8	6	260

* Given 100 cc. pig's bile on the day after operation.

† Barium chloride produced a slight rise in pressure.

Average pressure in cats after two days, 269.4 mm.; after three days, 281.6 mm.; in all experiments, 277.9 mm.

Stimulation of a sensory nerve, the saphenus, caused a slight rise in pressure in four animals, with a maximal change of 6 mm.

Injection of epinephrin caused no change in pressure. Section of both vagi caused no change. Bleeding the animal or injecting normal salt solution caused no change.

The pressure was taken in two dogs in which the common bile duct had been occluded two days, and was found to be 278 mm. and 292 mm., respectively. The dogs did not show any difference from the cats, except in the lower pressure in proportion to body weight. Stimulation of the splanchnics of Dog 2 did not cause any change in pressure.

Injection of 0.25 cc. of a saturated solution of barium chloride was tried on one dog and one cat. In the cat there was a rise in pressure of 3 mm. after each of two successive injections; in the dog there was a rise of 5 mm. after the first injection and 2 mm. after the second. Smaller doses produced no change. This dose proved fatal in each case after the third injection.

Why do the obstructed bile passages so often rupture after an interval of several days? Not because of any continued and progressive rise in the fluid pressure within them. Perhaps the best explanation takes into consideration the inflammation which may occur to a greater or less degree even after aseptic operations. The rupture may occur close to the ligature on the common duct, in one of the fissures between the liver lobes where the ducts are close to the serous surface, or in some part of the gall-bladder.

These experiments show that in chronic obstruction of the common bile-duct the pressure rises no higher than in acute obstructions. It may be even higher at the end of three hours than at the end of three days, but probably there is little variation. There are individual variations which we do not attempt to explain. There is no relation between the pressure and the weight of the animal.

It seems relatively safe to assume that the pressure rises sharply during the first three hours after obstruction. After this time the pressure remains fairly constant, but is the resultant of two factors: (a) secretion by the hepatic epithelium, (b) absorption by way of the hepatic veins. Whether the bile escapes by rupture of bile canaliculi, or by diffusion from the distended channels, is an open question, but it is known that the bile pigments and probably the other elements of the bile are removed from the liver of obstructive icterus by the blood vessels rather than by the lymphatics, which play an unimportant rôle (Whipple and King).²

We may say with considerable certainty that there is a given pressure for each animal, usually between 250 and 350 mm. of water, at which the secretion and the absorption of bile are in equilibrium. In whatever manner this chronic biliary obstruction may react on the liver cells, it does not greatly influence the pressure within the ducts.

² Whipple and King: Jour. Exp. Med., 1911, XIII, 115.

WILLIAM TULLY, OF CONNECTICUT, 1785-1859.

By KATE CAMPBELL MEAD, M. D., Middletown, Conn.

During the last years of the eighteenth century and the early years of the nineteenth there was great medical activity in Connecticut following the religious and political excitement of the Revolutionary days. It has been said that Nathan Smith, William Tully and Jonathan Knight were then to Connecticut, as doctors, what Ellsworth and Trumbull and Sherman were as statesmen. There were, indeed, at that time false prophets among the doctors, like the Perkinses and Thomsonians, but, on the whole, the medical affairs of Con-

necticut were guided steadily toward the establishment of the State Medical Society in 1792, and the founding of the Yale Medical School in 1813, after which her physicians became leaders in their profession in the United States.

Many of Connecticut's early practitioners had not received much medical education, and very few had studied in Edinburgh, like some of the Boston doctors, but they were what Cotton Mather called "Angelic conjunctions of Physic and Divinity." These "philotheloiatironomoi" exercised their

skill in matters spiritual as well as physical, although being farmers they often had to plough or make hay by daylight, and visit the afflicted at night. There were both Whigs and Tories among them, and during the Revolution they had taken their share of military service as commissioned army surgeons or colonels, with the same zeal as they showed later in the War of 1812. Thus they knew no idle hours, for, although most of the large towns were situated on the Sound or on rivers, where travel by water was easy though tedious, the philo-theo-medicos almost lived in the saddle, carrying a Bible and medicines in dirty saddle bags, and reading, if it was daylight, "every known author." In addition to all these occupations, men like the great Dr. Nathan Smith carried on an itinerant medical school, teaching their pupils botany and materia medica by the roadside, and instructing them in surgery and therapeutics by the bedside of the patient. It was in this way that William Tully, the subject of this paper, studied with Dr. Smith, in 1808 and 1809, not only learning how to use setons and cups and leeches, the actual cautery and blisters and the lancet, surgical instruments and drugs, but also taking an interest especially in the diagnosis of diseases.

Of William Tully's ancestors we know very little except that they had lived for generations at Saybrook, on Long Island Sound, having come from England in 1647. One of them is mentioned in the Chronicles of the Pilgrims because "he like to have sounded with cold," and was in danger of scurvy. Tradition tells us that the Tullys, or Tillys, were noted for their skill in fighting the Indians; and we may infer that some of them were "natural doctors," for a Tully is said to have made the profound remarks, "no one ever sneezes in a settled fever," and "no one ever catches cold unless he catches heat first"; their remedies for these diseases being hot saffron tea, blood-letting, and a few Indian medicines.

Our William Tully's father was Colonel William Tully, a Revolutionary soldier, who married his cousin Eunice Tully; by this close relationship, it has been suggested, we may account for the irritability and idiosyncracies of their only child, who was born in 1785. That the boy was delicate we learn from a letter of his daughter in which she says: "My father barely lived for 20 years. He was trained for college by Parson Hotchkiss, but he did not succeed in arithmetic, and failed to take the valedictory on that account. In all other subjects he was the smartest in his class." This, unfortunately, is all we know of William Tully's early life, but from various sources we gather the essential data of the subsequent years.*

In 1806 he graduated from Yale College and began teaching in the Oyster River School, near his home. The terms were not long, and during the next two years Tully alternately taught in district schools and "read medicine," while collecting an herbarium from the fields and meadows in the country near at hand. The first medical teacher with whom he took any definite work was Dr. Mason Fitch Cogswell,* of Hartford, a

famous physician and surgeon, who was said to have once amputated a thigh in 40 seconds.

In 1808 and 1809, as we have seen, Tully studied medicine with Dr. Nathan Smith in Hanover, New Hampshire. Of these years we hope to have the details when his diary is published. The following year Tully was again teaching school in Saybrook and studying with Dr. Samuel Carter, while at the same time he was taking a course in materia medica with Dr. Eli Ives in New Haven. It was this last subject which determined his career, because of his fondness for botany and his delight in Dr. Ives' wonderful garden of medicinal plants.

In 1810, his medical courses finished, Tully obtained a license to practice in Connecticut, and he was "called" to Enfield to begin his life work. He at once fell in love with Mary Potter, a doctor's daughter, but an attack of typhus fever debilitated him so much that he had to go home to recuperate. There he found his father dying, the family affairs needing attention, and so many questions to settle after his father's death, that his marriage was postponed until 1813. At that time he accepted an invitation to settle in Milford with his bride; but practice was slow in growing, and Tully spent more time in the fields, botanizing, than with patients; so that after two years of professional discouragement, they moved to Cromwell, which seemed more promising. This was in 1815, and it marked the beginning of Tully's success as a physician. His colleagues recognized his superior ability, and patients praised his skill. Three years later, cheered by these experiences, he decided to move to Middletown, a few miles down the Connecticut River, which at that time was one of the largest cities in the state.

While practicing in Middletown, 1818-1824, Tully attained considerable distinction as a physician and was much sought for as a consultant. He was at once appointed clerk of the County Medical Society (founded in 1792, one month earlier than the State Society), but we find only one record signed by him. This entry was dated 1818; it is simply: "Voted to adjourn to the parish of Potapaug in Saybrook, to the house of Danforth Clark, or to the next nearest tavern, or to the meeting-house in said parish." Nothing could be more concise. He was also appointed to "perform" at one of the meetings, but there is no record of his performance. We find, however, that the topic of church going was discussed about this time, and it was solemnly voted that the members should endeavor to attend public worship on Sundays. Moreover, it was voted that the society should not use ardent spirits at its dinners; thus signifying its disapproval of alcoholic beverages, a great step in those days when at each house a doctor was expected to have a drop of whiskey before seeing the patient. This prohibition motion was, perhaps, made by Tully, for his daughter, in a letter says: "My father never used tobacco, he despised it and whiskey too. He never took whiskey only when he came home very tired, and he always talked temperance."

The year after Tully settled in Middletown he received an honorary degree of M. D. from Yale College, where his medical teachers, Dr. Smith and Dr. Ives, were now professors. The following year, 1820, he published in the *Middlesex Gazette*

* Dr. Cogswell is remembered as the founder of the Hartford Asylum for the Deaf and Dumb, now known as the American School at Hartford for the Deaf.

his first long medical article. This was on the subject of scutellaria and its alleged curative effects in hydrophobia. In a rather dramatic manner he recites the history of a young girl of 14 years, named Mary Tice, who had suffered for 20 months from an unhealed wound of the hand. Then, suddenly being taken ill with fever and vomiting, she told her parents that a black dog had bitten her hand. Seeing their consternation she began to bark and to "go into convulsions at the sight of cold water." Many doctors who saw Mary in these attacks "gave her up," because she could swallow none of their medicines. Finally a new doctor saw her, bled her freely, administered 60 grains of calomel, soon had her drinking a quart of an infusion of scutellaria every 24 hours, and cured her in 6 weeks. Tully gives this story in more than 7400 words, printed in eight long columns of fine print, and he argues that since there was no authentic medical testimony that Mary Tice had hydrophobia, and since scutellaria had never been proved to have any medicinal value whatever, his own diagnosis is that the child had hysteria common to her age. This gives him an opportunity to hurl invectives at physicians who rush madly after new and untried remedies, and to condemn all newspapers which publish sensational but unauthenticated reports of cures of extraordinary diseases by newly discovered drugs. Toward the close of the article Tully, with ill-concealed sarcasm, offers to drink three pints of infusion of scutellaria every day for a twelvemonth to prove that it is as inert as common Bohea tea, and he advises the laity to keep scutellaria among the safe and common dried plants in their garrets, along with mint and mother-wort, sage and catnip.

Soon after the preceding article was published Tully was appointed to read a dissertation before the Convention of the Connecticut Medical Society at its meeting in 1822. His topic was "The Yellow Fever in Middletown in 1820." This dissertation formed a portion of the *Essays on Fever*,² published in 1823, by William Tully and Dr. Thomas Miner, one of his colleagues.

There had been 35 cases of yellow fever in the lower Connecticut Valley in 1820, fifteen of which had been in Middletown, caused, it was thought, by decomposing vegetables and filth from a vessel at anchor at one of the wharves. Tully, however, was not satisfied that the origin of this disease had been found, and he says, "The causes of the rise, progression, diffusion, and final extinction of epidemics are, in our opinion, involved in impenetrable obscurity—at least in the present state of medical science. We hope that the period will soon arrive when the medical profession will no longer esteem it an evidence of wisdom to affect to know what they are in fact ignorant of, and to consider themselves as bound in duty to supply by hypothesis what they lack in knowledge." (p. 459.) And again (p. 348): "Yellow fever will forever remain one of the most unmanageable and fatal of diseases to which mankind is subject. . . . For, since it is a part of the scheme of Providence that men shall continue mortal, it is probable that epidemic diseases will ever be a great instrument in producing this mortality." In this confession of ignorance Tully was in

accord with Dr. Nathaniel Potter, of Maryland, who, in 1817, after trying in many ways to take yellow fever from his patients, said: "It comes, they know not whence; and goes, they know not where. Pursue it as they may, it must still elude their grasp, vanish with circumbient air, and like the baseless fabric of a vision, leave not a trace behind."³ There had not been such skepticism as to the causes of contagion when Tully was a boy, for Noah Webster, in 1794, had proved to his own satisfaction, and apparently to that of the world, that an epidemic in New Haven was caused by "decaying shad which had been thrown into the dock," to which was added the odor of rotten clams and of a barrel of pickled codfish uncovered at low tide. But 25 years allow time for great changes in medical ideas, and, while doctors agreed with Currie, of Edinburgh, that contagion spread by laws peculiar to itself, they hardly dared accept the theory that it was an airborne disease, and abandon quarantine against it.

Therefore, obliged to leave undiscovered the causes of fevers, Tully discusses their symptoms, and for the sake of simplicity in treatment, he divides all fevers into two classes. These are "putrid fevers, including jail, ship, or hospital fever, which bear bleeding well," and nervous fevers, including spotted fever and pneumonia, "in which bleeding would never be tried but for the rash surgeons, who since the war of 1812, had bled all their patients." For these latter fevers Tully strongly advises against using any depleting measures, such as, for instance, an emetic repeated as often as a patient stopped vomiting. He quotes one case where 70 grains of tartar emetic had been given until the patient was almost dead, and this was followed by as large doses as the stomach would bear of cinchona, camphor, sulphuric acid, ammonia and ether.

"Dashing practice" was evidently the order of the day. Tully says, "The lancet has annually slain more than the sword, and antimony has done more injury than all the efficient exciting and supporting agents of the materia medica. The King of Britain loses more subjects each year from these two causes than the campaign of Waterloo cost him." (p. 461.) But even Tully was as extravagant himself in the use of "exciting agents" or "stimulants" (?), among which were calomel and opium. As regards these drugs he believed that the timid physician was the patient's worst enemy; and he tells his readers how to give these remedies: "More than 1000 grains of calomel may be given in the preparatory stage of yellow fever, and a proportional quantity of mercurial ointment applied externally, not only with safety, but with the most complete success, for neither weight nor measure is to be at all regarded till there is an alleviation of the disease." But he adds: "If calomel is not given in the first stage of the disease, it should not be given at all." (p. 335.) As to the use of opium, it was to be given "steadily, resolutely and perseveringly, at short and regular intervals, in such quantity as to allay all the pain and irritation, and to support the powers of life." (p. 329.) As to the dosage, he says, "It requires not more than seven or eight grains of opium in 24 hours to keep 100 grains of calomel from running off from the bowels." He often gave 60 grains of calomel the first day in the form

of a syrup," not desiring to cause pyralism by the mercury, or a soporific effect from the opiate," as, in fact, he had noticed that the opium often mitigated coma or stupor. If any physician doubted that this was the very best treatment of fevers, Tully considered him "timid, desultory and skeptical, and not able to make observations with sufficient accuracy to gain any useful experience."

In the use of alcohol it would seem to us that Tully was even more "dashing." "To the sunken cases," he says, "I give great quantities of spirits. . . . From two pints to a gallon of whiskey in the 24 hours, with the happiest results." He adds that he has never known intemperance to be caused by any spirits given in sickness, but he says, "I believe that the liquor of the arsenite of potassa in half-drachm doses would have done as well, or laudanum in drachm doses every half hour for several days."

In the light of the twentieth century we are not surprised that the advocacy of such dosage, even in contemporary times, brought forth much adverse criticism of Tully's therapeutics.* But criticism he never could endure, and so great was his irritation at the unfavorable comments of his colleagues that he was unwilling to live in Middletown among them any longer; consequently, in 1824, we find him settled in East Hartford where he already had many friends in the profession. Here lived his first teacher, Dr. Mason Fitch Cogswell, who had declined the chair in surgery at Yale, and Dr. Eli Todd,[†] the founder of the Hartford Retreat for the Insane, and many another choice spirit. Together they formed a social club in memory of that "wit among poets and poet among wits," Dr. Lemuel Hopkins, who had died in 1804. They took their wives with them when attending the meetings of this club, often riding 10 or 15 miles on horseback to the homes of the various members.

In the society of such congenial colleagues Dr. Tully should have been contented, but, having accepted the chair—"settle" rather—of materia medica, and theory and practice of medicine, besides the presidency of the new Vermont Academy of Medicine, at Castleton, a few miles south of Rutland, he was obliged to be there for 14 weeks each year. This enforced absence caused grumbling and criticism among his patients and colleagues in East Hartford; and the ever intolerant Tully, in less than two years, decided to move to Albany. His wife, although somewhat of an invalid, had borne him eight children, of whom six had died in infancy. History fails to tell us how she liked these uprootings, but most wives were patient in those days, and therefore to Albany they went, where the doctor became a partner of Dr. Alden March. This

* Forty years later Oliver Wendell Holmes said, "Dr. Hooker believes that the *typhus syncopalis* of a preceding generation in New England, was often in fact a brandy and opium disease."⁴

† In 1822-1824 Tully was one of a committee of three that drew up the Constitution of the Hartford Retreat, pushed the bill through the legislature, and raised the money to start the Institution. Dr. Todd was the chairman of the committee, but Tully's energy was needed to supplement the pathos and logic of Todd's oratory.

arrangement lasted, however, only three years, for in 1828 Dr. Tully received an invitation to fill the chair of materia medica and therapeutics at Yale, made vacant by the resignation of Dr. Ives. He accepted the call, and the family moved to New Haven in 1829. The following year twins were born to them, making 11 children in all, of whom only four lived to grow up. These children were educated in New Haven, their home for 20 years. During 14 of these years Dr. Tully lectured both in Castleton and New Haven, having larger classes in each of these schools than were found in any other institution in New England. Moreover, it was said that most of his advanced students "worshiped him"; but the younger ones found great fault with his style, and they criticised him so continuously that he felt that he was wasting his time in trying to teach them. Tradition tells us that, dissatisfied with his compensation, and irritated at the never-ending agitation against him by colleagues and patients as well as students in New Haven, Tully handed in his resignation about once a year, until finally, in 1841, the authorities at Yale accepted it, probably much to his chagrin.

What these criticisms of pupils and colleagues and patients were, we find in an account of the life, as a Yale medical student, of Dr. F. W. Mathewson, of Durham, who was graduated in 1833, in a class of 69. He tells us that the poems to Tully's descriptions of drugs were too long and tiresome; that one lecture often filled 90 pages; that his repetition of Latin words and phrases made the taking of notes difficult; but, notwithstanding this verbosity, and an irritating vehemence in denouncing popular treatment by the lancet, and antimony and other reducing agencies, the older students found him interesting, and they learned more practical medicine from him than from any other teacher. Tully's colleagues also found fault with him for his denunciation of their "dashing treatment." And, one by one, his patients turned from him to more tactful, if less learned doctors, and his colleagues even refused to have him in consultation because he had so frequently said that he preferred to talk himself rather than to listen to their "prattle." He often spoke disparagingly of patients' "garrulity," and called it "medicina anilis." Moreover, other members of the faculty thought his courses too severe in comparison with theirs. We wonder what some of the other courses were, for there were none at all in organic chemistry or urinalysis, or in auscultation and percussion; and only half a dozen lectures in gynecology with no demonstrations of the vaginal speculum. The microscope was new and to be looked at, not through. The new hospital furnished no clinical material, and the use of the fever thermometer was not considered worth while for the occasional patient. On the other hand, surgery was well taught by Dr. Nathan Smith, and anatomy was elucidated by means of an occasional body snatched from the grave, and, according to Dr. Smith, "hewn in pieces as Samuel hewed Agag, but for a different reason." Therefore, if Tully's courses seemed severe, it was because of his breadth of vision. He meant to impress his pupils with the necessity for exactness in prescription writing and compounding. It was important for them to know Latin, the universal medical language; and it was a *sine qua non* that they should

not combine incompatible drugs or prescribe "shot-gill" doses.

Surrounded as Tully was, therefore, by so many opponents, and convinced that his compensation was in every way too small, he can hardly be blamed for resigning his position at Yale. We do not know what his salary was, for it was paid directly by the students at \$12.50 per capita, and from other funds of which no record remains; but it could hardly have been less than that which Dr. Smith received for his courses at Bowdoin College, which was \$100 a week for a six weeks' course. As for medical fees, Dr. Smith said: "The people of Connecticut have no idea of rewarding professional men except by compulsion or by being begged. The lawyers compel and the priests beg for pious purposes." The usual charges for medical services, however, were "two shillings for a day visit, four for a night visit, one for a mile travel, one for a puke, one for a purge, one for bleeding," etc. These charges always included all necessary medicines prepared by the physician.

Having, therefore, lost his salary from both Yale and Castleton (where he had resigned in 1838), and not being afflicted with too many professional fees, Dr. Tully was undecided what to do next. He had already begun to suffer from some affection of the bladder which caused his death 1¹/₂ years later, and therefore the state of his health may have prompted him to go to Charleston in 1842, possibly to settle there if everything should be to his liking. He had refused a call to the University of South Carolina in 1833, where he may have still had friends, but there seemed to be no opening at this time in that warm climate; and so, disillusioned once more, he went back to New Haven the next year to pick up what practice he could and prepare his "briefs" for publication. Finally, in 1851, the family moved to Springfield, Massachusetts, where these briefs of his monumental work, the *Materia Medica*, were to be printed.

It was in Springfield, in 1853, that Dr. Tully's wife died; and he himself, in 1859, "*plenus annis, ex hac vita migravit.*" He left a small estate to his three surviving children, but his library of 2000 volumes and his instruments were sold at auction for a small sum, "a mere song," his daughter says; and, as his manuscripts had no pecuniary value, they were given to one of his students. Two volumes only of his great *Materia Medica* were finished, and they were too encyclopedic to sell profitably.

Discouraged with life, a short time before he died Tully had said: "It is well known that the emoluments of the medical profession are by no means in proportion to the amount of work done, and as for medical schools in New England, they diminish rather than increase the income of the instructors; at least such has certainly been the fact as concerns myself, for I have wasted my time 16 years in one institution (Castleton), and 14 in another."

Such, in brief, are the main facts in the life of William Tully. One of his friends, Dr. Miner C. Hazen, gives us this picture of him: "Tully was a large man, tall and broad, with a wide head and prominent eyes, and would have been a man to attract attention anywhere without the gift of speech. I re-

member him well as he used to fill the large armchair in H. J. Brewer's drug store, in Springfield. He seemed to be perfectly happy if he could get a doctor or two to listen to some of his learned talk, generally on some article in the *materia medica*. At such times he did all the talking in a loud voice with an assured manner. The world itself could hardly have held all the books he would have written if he had had the opportunity."

Of the accompanying portraits of him, Tully's daughter says: "The lithograph was considered very good when he lived in Hartford, and the daguerreotype was a fine likeness of the noble man." Continuing her reminiscences, she says: "My father was a very warm-hearted man and thought a great deal of his family. He had no hobbies and no musical talent, he rather laughed at such things, but he was fond of poetry and would read it beautifully; he never cared for any other recreation, only reading. He loved children and would trot them on his knee, and they always expected it and called him 'dooor.'"

From contemporary writers we may also draw an imaginary picture of Tully as he went on his professional rounds. He always carried in his vest pocket a small bunch of papers which he called "octets." Wherever he was, on the street or in the sick-room, if a thought struck him he wrote it down at once on an octet, whether he interrupted a patient's tale of woe, or was dosing a child for diphtheria with his favorite remedy, turpeth mineral. His study of drugs required careful notes at the bedside, and his lectures demanded of him great accuracy in recording the effects of his remedies. Therefore, he says: "If the dio-proto-sulphate of mercury does not operate in an hour, give ipecac to quicken it. The second or third act of vomiting generally brings up the membrane." Probably then, while the croupy baby was struggling for breath Tully was taking notes on this "most slandered drug," or pompously trying to impress the poor mother with his wealth of knowledge, for it is said that he could describe diseases with great unction, but sometimes fail to recognize them clinically. Perhaps it is well that he had no Boswell.

But if Tully had faults, he also had many virtues which scholars could appreciate. Dr. Bronson⁸ said that he knew botany and chemistry better than anyone in the United States, and it was this knowledge which gave him an association with the early editions of the *National Pharmacopeia*. It had chanced that when Tully was taking his medical course with Dr. Nathan Smith, in 1808, Dr. Lyman Spalding was in Hanover, New Hampshire, agitating the question of a United States pharmacopeia. Tully was evidently impressed with the necessity for such a work in place of the clumsy formularies which each state had compiled for itself, and after he had finished his studies, while Dr. Spalding was bringing the subject before the medical societies of New York and some of the New England states, Tully frequently advocated the matter in Connecticut. Time was needed, however, to discuss the elimination of certain drugs which, though proved to have little value as medicines, yet had always been in the list, together with the long special prescriptions which had been handed down from past generations. At length, in 1817, the

New England societies voted to hold a conference in Boston, in 1818, at which delegates from all these societies and the medical schools should meet to discuss the question. From the members of this convention 12 delegates were elected to go to Washington in 1820, to compile a national pharmacopœia. These delegates, according to the instructions they might receive from their own states or colleges. Tully was among the delegates to the conference in Boston, but he was not sent to Washington, and, therefore, he had only an indirect share in the preparation of the first edition. Ten years later, however, he was one of the 10 delegates who met in New York to revise the first edition "in accordance with the present advanced state of science."⁶ This must have given him great pleasure, and he doubtless seized the opportunity to suggest substituting his camphorated opium powder for the old-fashioned Dover's powder, but we do not find it in the accepted list of formulæ.*

While in his prime, therefore, Tully must have led a busy life, but he found time to write a good deal for the medical journals, and among his articles we find the following titles: Ergot (1822); Datura, Sanguinaria (1828); Ferns growing near New Haven; Narcotine and Morphine; Actæa Racemosa; Chlorite of Potassa; and Congestion. For these articles, his daughter says, he was so "persecuted that he refused to publish others." Probably the persecution was nothing more than ordinary criticism, but, as we have seen, Tully did not take kindly to that sort of discipline. After retiring from such active work, however, he was persuaded to compile his briefs, and publish his masterpiece, the encyclopedic *Materia Medica*.⁷

The introduction to this work occupies 365 pages, the classification of drugs 83 pages more, and there were finished 1534 pages in all, a small part only of the contemplated work. This prolixity was due to the immense number of drugs which were supposed to have medicinal value. Tully said: "Even on the grounds of substitution an extensive catalogue may be not only useful but important, taking the circumstances of time, cost or availability into consideration." Surely Tully's ideals were high, for his motto was, "A doctor should never be satisfied until he knows everything that can be known." His plan was, then, to catalogue all the articles of the *materia medica* which the physician should have at his command, comprising, (1) "Every indigenous remedial agent which is definitely known to be capable of being useful in the treatment of any cases of disease; and (2) every exotic article of the same general character that can be conveniently obtained and easily kept."

Tully, we see, did not believe with Lord Bacon that a multiplicity of remedies is the child of ignorance, for he says

* The formula for the Tully powder was as follows:

Morphinæ oxydi sulphatis, gr. j	} aa gr. XX.
Camphoræ officinarum,	
Radicis Glycyrrhizæ officinalis,	
Calciæ Carbonatis mollioris preparati,	

This powder was to be so divided that 10 grains contained 1/6 grain of morphine. For its preparation Tully gave minute directions, having no confidence in the judgment of doctors or pharmacists as to the quality of the ingredients or the care with which they should be mixed.

(p. 295): "It appears to me that the educated, graduated, licensed, or as he is so fondly called, the regular practitioner, who habitually treats every variety of case of all species of disease, with a very few articles of medicine, is in no respect better than the uneducated, non-graduated, unlicensed and irregular quack, who does precisely the same thing." He scorned the great Abernethy's skepticism of drugs, and he says of him: "Apparently it would have given Mr. Abernethy no deep concern, if all the articles kept at Apothecaries' Hall had been washed away in a general deluge of pharmacy. The blue pill, Plummer's pill, the infusion of gentian and senna, and the decoction of sarsaparilla, were almost the only preparations which he would have admitted into the Ark."

As Tully's belief in drugs was firm, so he was strong and long in discussing them. He enumerates the effects of each one and gives the results of his experiments with it. As he did not believe in hypodermic medication, so he also scorns the idea of injecting medicines into the veins, especially "a pint of brine, an antiphlogistic cathartic which makes no part of the natural circulatory fluids." He says (p. 265): "This foolhardy operation could never be done by any physician in his senses." Nor does he think that a competent observer would conclude that experiments on animals could lead to any correct estimate of the effect of such drugs on human beings. There are many pages of lengthy arguments concerning proofs of experiments which do not stand the test of time.

In definitions, too, Tully was painfully discursive. He had defined many words for Webster's Dictionary (editions of 1840 and 1847), and these—anatomy, physiology, botany, for example—he had defined briefly and to the point, but in his *Materia Medica* he was not limited by time or space. Common oil of wintergreen is "Ol. Pyrolæ, a true saline æther, the spirhylate or oxyspirhylate of protoxyd of methygen, existing naturally in the plant *Gaultheria procumbens*." The word *adenagic** is defined in one hundred and eighty words; the explanation of the action of drugs belonging to the class *adenagica* occupies sixty pages; and each drug in a class, such as mercury, the iodides and the bromides, also requires long discussions. Is

* Mat. Med. p. 1126, Vol. I, Part 2.

Definition.—*Adenagics* are articles which exert a direct, an especial, a peculiar and a specific operation upon the secretents and absorbents or the glandular system generally, by which a greater or less change of action and condition is produced—a change manifested by a direct resolution of certain chronic, subacute atonic phlogoses or inflammations; certain parabysmata and glandular enlargements; by the obviation of certain dysthetica; by the improvement of certain vitiated ulcers; by the relief or cure of certain cutaneous diseases; by the obviation of torpor and inactivity of all the secretories and excretories; and as is commonly said, though I think incorrectly, of the secretory apparatus of the liver; and by a consequent increase of the secretions and excretions, and as is commonly, but I think erroneously, believed, more especially of the biliary than of any other, and also by a diminution and improvement of the secretions and excretions where they are excessive and vitiated; the whole independent of any change in the degree of the vital energies or the strength of the action of the sanguiferous system, and not caused by any evacuation which may happen to be produced.



WILLIAM TULLIA, M.D., 1827.



WILLIAM TULLIA, M.D., 1859.
(Taken at age 1841.)

it any wonder that Tully's students had rebelled at the work he gave them if his book is a sample of his lectures? He stops in the middle of a long definition to condemn the general looseness of medical phraseology, and to berate the unscientific doctors who used words which their patients could not understand. He insists upon calling catarrhal bronchitis "idiopathic pleynorrhoea bronchialis"; catarrh of the urethra, "urethritis pyro-blennorrhoea"; etc.; but for these many-syllabled diseases he tells us there is no cure, since there are no "true expectorants, aposthetics or chremptics" (p. 1259.) This was surely a disheartening avowal for those days when there were few therapeutic nihilists, and fewer patients who did not expect to take large doses of medicine in order to be properly cured.

But however long-winded Tully was in his *Materia Medica*, and however egotistic in his treatment of disease, "The imperfections of the work are all forgotten," Dr. Bronson says, "by him who has the capacity to understand it." Even in our day it should be regarded as a classic in its unfinished state, and it is most unfortunate that the intervals of its publication were so often lengthened by the illness of the author, and that his death, in 1859, ended the work so abruptly. There was no one able to carry it through even with the "briefs," but the sales were not assured, and the few copies which had been sold are probably seldom used even for reference, although the work is full of interesting information collected from all over the earth.

It is idle to conjecture what William Tully might have achieved under more favorable conditions, although he is seen

in truer perspective now than in his own times. We have seen enough, however, to show that he stood far above the rank and file of his contemporaries, for, as Dr. William H. Welch⁸ has said, "He was a really remarkable man, erudite, original, an experimentalist unrivalled in his knowledge of the *materia medica*, and an extensive contributor to medical literature."

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

NOVEMBER 1, 1915.

1. Exhibition of a Case of Benzine Poisoning. R. L. HADEN.

This patient was admitted to the hospital on October 4, 1915, complaining of weakness and dizziness. He is 42 years old. His family and past history have no bearing on the present illness. Since July 14, 1914, he has been working in a lithographic establishment in this city, where he was employed in cleaning the lithographic rolls with benzine. In this work he has a trough about 6 feet long and 1 foot wide, filled with benzine, in which the long rolls are dropped and cleaned. He has worked at this for a variable number of hours, averaging about 5 hours a day. He has been using about 2 gallons of benzine a day, all of which evaporates. The work is done in a very large room, but to keep the lithographic inks from drying, the room is without ventilation.

After about 2 months of this work, he began to have quite severe nausea, vomiting and dizziness. The symptoms were progressive. About the same time he had a peculiar feeling in his head, which was not a definite headache, but what he describes as a "sense of compression" or "a pressing-in feeling." He was also getting weak. On account of these symptoms he left off work after two and a half months and went to a hospital in Washington, where he had been operated on three years previously. After staying there three weeks, the condition largely cleared up. He returned to Baltimore and went back to work. The symptoms rapidly returned and since that time he has been able to work only about

4 days a week. The symptoms have been as follows: He has had nausea, vomiting, dizziness and a peculiar sense of compression in his head continually. Later drowsiness developed. He was so drowsy that he often had to stop his work and wash his face in cold water in order to stay awake. There was a sensation of heaviness in his limbs, his legs feeling "like bags of cement." In addition, there was coldness in his legs, a feeling as "though menthol had been rubbed on them." He had some pains in his legs and arms, the pains in the arms being associated with a cramp of the muscles and ending in a marked hypertension of the fingers. He noticed also dimness of vision and twitching of the eyelids. Meanwhile, his weakness had become so extreme, that whereas formerly it had taken him only 15 minutes to walk from his home to work, it now took him about an hour. Very often, he says, he would feel as if he were walking, when, in fact, he was not moving at all. Several times he fell on the street. Five weeks before he came into the hospital, he noticed that his urine was becoming dark and had a peculiar odor. Two days before admission someone told him he was jaundiced. For some time he has been troubled with spontaneous contractions of the muscles of the legs and arms, which often awakened him at night. On account of these symptoms, he had to stop work on the 27th of September.

On admission, he was a fairly well-nourished man, but so dull that it was difficult to get a history from him. He seemed to be unable to speak or to think clearly. There was a very peculiar color to his lips, which seemed to be a combination of an intense cyanosis with the jaundice, giving a peculiar purplish tint. There was a peculiar odor to his breath, which did not resemble that of

benzene, but was rather sweetish. His lungs showed signs of chronic fibroid changes at the apices, without any evidence of activity. The liver was 2 fingerbreadths below the costal margin and tender on palpation. The spleen was easily felt. There was marked tremor of the eyelids and tongue. All the deep reflexes were extremely active, as were also the superficial reflexes, and there was a very marked contralateral patellar reflex. There were no clonus, fibrillary tremors or muscular atrophy. The plantar response was normal. There was no spasticity. On sensory examination, no change was made out. The blood examination showed 4500 white and 4,300,000 red blood cells; hæmoglobin 70%. The differential count was normal. Two gastric analyses showed a slight hyperacidity; the stool was normal; the urine was almost black with bile, and there was a trace of albumin. The Wassermann and Calmette (1% and 5%) tests were negative.

Since he has been in the ward he has cleared up mentally, and the cyanosis and jaundice have both disappeared. The peculiar odor of his breath has also entirely disappeared and there is perhaps some improvement in the condition of his nervous system.

It seems fairly clear that this is a case of chronic benzene poisoning. We think this diagnosis is fairly definite because of his long exposure to this substance, and the fact that his symptoms have twice cleared up shortly after he left his work.

In 1901, four cases of chronic benzene poisoning were reported from the medical clinic in Berlin. Four workmen in a rubber factory presented symptoms similar to those in this case. There were nausea, vomiting, headache, dizziness, pains and sensations of heaviness and coldness in the limbs, with cyanosis and spontaneous contraction of the muscles. Jaundice was not described in any of these cases. However, there is one case of acute benzene poisoning reported, in which jaundice appeared in 24 hours. In two of the Berlin cases there was a peculiar change in the blood, free pigment appearing in the plasma and in the red and white cells. We have looked for free pigment in this case, but although we could note some in the plasma, we have not demonstrated it in the red or in the white blood cells. Dorendorf, who reported the Berlin cases, did a number of experiments on guinea-pigs, in which the animals were allowed to breathe the fumes of the benzene for short periods over a number of days. In these guinea-pigs pigment was found in the blood and a number of the symptoms referable to the central nervous system were present. On section, the guinea-pigs showed peculiar changes, mainly in the anterior-horn cells; these showed a deposition of pigment and a large number of vacuoles.

At the present time the patient still has rather marked tremor of his eyelids and some tremor of his tongue. He still has very active reflexes and a contra-lateral patellar reflex. At times, while he has been in the ward, when the triceps tendon was struck, nearly all the muscles of the body would contract in a manner very strongly suggestive of a convulsion from strychnine poisoning.

DISCUSSION.

DR. FUTCHER: On a number of occasions I saw this patient in the ward, and I do not think there is any question but that he is suffering from benzene poisoning. Owing to rather severe pain in the upper abdomen, the question came up, on admission, as to whether he might have some chronic trouble, in addition to the possible toxic manifestations. He had been in Cuba, where he had a dysentery, so we had to keep in mind the possibility of his having an amebic abscess of the liver, although there were no physical manifestations. As he was jaundiced, we had to keep the possibility of gall-stones or chronic cholecystitis in mind also. I think Dr. Haden was strongly impressed from the beginning that we had to do here with a case of industrial poisoning, and Dr. Janeway, when he saw the patient a few days after admission, was also firmly convinced that his symptoms were essentially those of benzene poisoning.

If one reads Dorendorf's article in which the two cases are reported, and compares the symptoms with those presented by this patient, one finds they are practically identical with those described here. Benzene is not as pure a compound as benzene is. It is the same as benzol, but with a mixture of hydrocarbons. The symptoms and physical signs are rather different from those we get in true benzol poisoning. The drug seems to exercise a special influence on the nervous system and on the blood. There appears to be, in some of the cases, an actual oxyhæmoglobinæmia. Dorendorf found that the spectroscopic showed the two characteristic absorption bands between the D and E lines of Fraunhofer's scale. Both patients presented these features. I do not know whether a spectroscopic examination was made in our case. The patient has been in the ward some time and it is doubtful whether the blood would show the changes at this time.

The striking features in this case were his physical weakness, mental hebetude, the cramps in the muscles, the nausea and vomiting, and the oppression in the head. The exaggeration of the knee-jerks was very striking from the beginning. A good many of the cases reported not only had the oscillation of the eyelids, but tremors of the muscles in general.

What causes the pains in the extremities is a matter of doubt. Whether or not they are in direct relationship to the changes in the central nervous system, I do not think has been definitely determined.

It is rather interesting, that in this hospital we have had several cases of benzol poisoning, with a fatal termination in two of the cases. Several of the patients recovered; the most recent case was here about a year ago, and recovery followed after several indirect transfusions. I think we have here the first case of undoubted benzene poisoning in the records of the hospital. Oliver, in his interesting book on "Dangerous Trades," has quite a long chapter on benzene poisoning. His cases occurred chiefly among workmen in powder and explosive manufactories in England, where benzene, particularly in its nitro compounds, is used in the manufacture of explosives. The symptoms present were very similar to those which this patient had, and which Dorendorf reported in his two cases.

DR. MILLER: There seems to have been a little doubt as to this case being one of benzene poisoning. There could be no doubt about the poisoning by kerosene in one of the first cases to be admitted to the Phipps Psychiatric Clinic. This patient, having made his escape, swallowed the contents of a bottle holding about two quarts and a half of kerosene before he was rescued, so there could be no doubt as to the lesions which subsequently developed. It is rather interesting to note that this patient, who presented a hypermanic type prior to the taking of the kerosene, lapsed into the extremest condition of hebetude. As he slowly emerged from this, he showed clinically, more or less, the symptoms described in this benzene case. He complained for a long time of the curious sense of oppression in his head. He could not walk, and, over a period of about six weeks, was definitely jaundiced. During that time the urine was extremely dark, and it showed the bands of oxyhæmoglobinuria when examined spectroscopically. Apparently the two poisonings may be more or less analogous.

2. The Interpretation of a Positive Nitrogen Balance in Nephritis.*

HERMAN O. MOSENTHAL.

In the study of nitrogen metabolism, in certain cases of nephritis, a retention of this substance was observed. The conception of the retention of nitrogen in nephritis, as understood by the clinician, generally implies two facts: Firstly, that a marked positive nitrogen balance is usually due to kidney insufficiency; secondly, that

* From the Medical Clinic of The Johns Hopkins Hospital. Baltimore.

the retained nitrogen is present in the body as waste nitrogen and circulates in the blood, in part, at least, as non-protein nitrogen. It is known from the work of Marshall and Davis† that urea is evenly distributed throughout the body, except in certain tissues, as the fat, bone, cartilage, etc., which do not take up urea. In calculating the theoretical amounts of non-protein nitrogen to be expected in the blood, it has been assumed in the present series that all the nitrogen which the body has metabolized, and is about to excrete, in contradistinction to the nitrogen which the tissues are storing, is evenly distributed throughout the body, as is the case with urea. Applying these principles to the total non-protein nitrogenous products, it is found that in a subject of average weight, for every gram of nitrogen retained, the non-protein nitrogen of the blood should be increased 1.33 mg. per 100 cc. According to these calculations, in the cases presented here, if none of the retained nitrogen was assimilated or stored, and all of it circulated as waste nitrogen because the kidneys did not excrete it, the figures shown in the table would be obtained.

TABLE I.

THEORETICAL AND ACTUAL VALUES OF NON-PROTEIN NITROGEN OF THE BLOOD RESULTING FROM NITROGEN RETENTION IN CERTAIN CASES OF NEPHRITIS.

	N of blood, mg. per 100 cc.			N grams retained during observation.
	At beginning of observation.	At end of observation.	Theoretical value at end of observation.*	
Case 1	30	37	152	92.0
" 2	30	38	116	65.0
" 3	25	34	93	51.0
" 4	30	37	165	101.4
" 5	29	27	119	69.1
" 6	71	74	117	55.3

* These figures represent the values obtained for non-protein nitrogen of the blood at the beginning of the observation plus the theoretical value due to retained nitrogen.

This table shows that a positive balance of nitrogen, in cases of nephritis on a mixed diet, is not necessarily followed by a corresponding increase in the non-protein nitrogen of the blood. Similar results have in the past been obtained in normal individuals. However, in clinical medicine, such a course of events is not given the recognition it deserves. It is evident that discretion must be exercised in interpreting a normal figure for non-protein nitrogen of the blood, as indicating that no nitrogen retention has taken place, and in considering a positive nitrogen balance as an absolute indication of the inability of the kidneys to excrete this substance.

3. On the Treatment of Hay Fever by Vaccination with Aqueous Extracts of Certain Plant Pollens.‡ G. H. A. CLOWES.

The purpose of this paper is to give a brief report of the results obtained in the course of the last four years on upward of one hundred hay-fever cases, treated by means of repeated injections of the extracts of certain plant pollens. The pollens employed were first dehydrated by means of a mixture of acetone and ether, and subsequently extracted with water—a method which is vastly su-

perior to the freezing and thawing procedure of Dunbar, Noon and Freeman, owing to its greater simplicity and to the durability of the dry product. Although a large variety of pollens was tested, the majority of individuals were found to be sensitive to one of the two main groups: Gramineae, flowering for the most part in the spring, and Compositae, flowering for the most part in the autumnal season. Cases were tested by means of the ophthalmic and cutaneous methods previously described,† a flush being produced in the eye of a sensitive individual by the introduction of a drop of a solution containing from one part in five hundred thousand to one part in a thousand of the pollen, based on original weight.

Although a limited number of individuals are sensitive to the pollen of both main groups, and exhibit hay-fever symptoms in both spring and autumn, a majority are sensitive only to the plants of a single group. Group reactions are frequently obtained, different individuals exhibiting varying degrees of sensitiveness to plants in the same group, but it is almost invariably the rule that sensitiveness to ragweed will be associated with sensitiveness to goldenrod and vice versa, although it is perfectly possible for individuals sensitive to ragweed and goldenrod to be entirely free from any sensitiveness to more distantly related members of the Compositae family, dandelion for example, and vice versa.

A marked alleviation of symptoms and reduction in sensitiveness may be effected in the majority of cases by the injection of dilute extracts of the pollens to which the individual is sensitive, starting, preferably two or three weeks before the commencement of the season, with doses as small as 1 cc. of a one in five million to one in a million, increasing the dose at intervals of three or four days, until ten or twelve doses have been administered, the maximal dose employed being 1 cc. of a one in five thousand to 1 cc. of a one in a thousand. The results were controlled by comparison with untreated cases; and also by immunization of individuals sensitive to two widely divergent pollens against one only, thus proving the specificity of the immunity or desensitization produced.

Shortly after the conclusion of treatment sensitiveness once more develops, and within a period of from three to six months reaches a figure equal to that observed before treatment, but in those cases in which treatment has been extended over a period of three or four years, reduction in hay-fever symptoms is noted from year to year, which suggests the possibility that by continued treatment a cure may ultimately be effected. A certain number of cases exhibiting seasonal asthmatic symptoms, but without any of the other symptoms normally accompanying hay fever, have been considerably alleviated by pollen injections. From 25 to 30 per cent of the hay-fever cases thus far treated have experienced marked alleviation of symptoms. A further 30 or 40 per cent show a marked improvement, while the remainder are apparently entirely unaffected by the treatment. However, in view of the fact that cases of this latter type seldom exhibit any marked cutaneous or ophthalmic reaction, we are inclined to believe that we have not yet discovered the particular pollen varieties to which their symptoms are especially attributable. A non-specific immunization, or rather reduction in sensitiveness, may be effected in certain cases by administering large doses of calcium lactate. It is worthy of note that well-nourished individuals appear to respond most readily to treatment with calcium salts.

Sensitization attributable to other causes than pollens is occasionally confused with hay fever. We have, for example, observed

† Marshall and Davis: Jour. Biol. Chem., 1914, XVIII, 53.

‡ Lütjhe: Ztschr. f. klin. Med., 1902, XLIV, 22.

Lütjhe u. Berger: Deutsch. Arch. f. klin. Med., 1904, LXXXI, 278.

Von Noorden u. Krug: Arch. f. Anat. u. Physiol., Physiol.-Abth., 1893, § 371.

§ From the Biological-Chemical Department of the State Institute for the Study of Malignant Disease, Buffalo, New York.

‡ Clowes: A preliminary communication on certain specific reactions exhibited by hay-fever cases. Proc. Society for Experimental Biology and Medicine, 1913, X, pp. 69-72; also, A preliminary communication on the treatment of autumnal hay fever by vaccination with an aqueous extract of the pollen of ragweed. *Ibid.*

sensitization to a certain variety of flies, which was successfully treated by vaccination with a solution containing an extract of the flies in question. Marked cutaneous reactions have been obtained in the case of individuals sensitive to protein constituents of fish, horses, sheep's wool, apples, etc., from which it would appear that sensitization not only to pollens, but also to a large variety of foreign proteids, occurs more frequently than is generally appreciated, and is responsible, not only for hay fever and asthmatic symptoms, but probably also for certain gastro-intestinal and other disturbances of obscure origin.

The susceptibility to the development of sensitization phenomena appears to be, in a measure, an inherited characteristic. From data accumulated regarding certain families over a period of several generations, the occurrence of one or another form of sensitization occurs in such ratios as to suggest the advisability of further study in this direction. From the fact that cutaneous reactions are exhibited at any point in the body, and that a complement deviation reaction is frequently obtained in the blood, the sensitization in hay fever appears to be systemic, but all attempts to produce reactions in normal individuals, after incubating the pollen extract with the serum of a sensitive individual, have failed of result.

Attempts to produce immunity by means of a single dose of pollen extract do not appear to be very successful, from which we must conclude that hay fever differs essentially from ordinary protein sensitization.

DISCUSSION.

DR. FORD: I am sure you will all agree with me that the various phenomena connected with the problem of hay fever are in the main so complicated, particularly from the theoretical aspect of the subject, that it is extremely difficult to get a clear conception of it, and we are immensely indebted to Dr. Clowes for bringing out a number of points which are of exceptional value in its consideration. We take a great interest in hay fever in Baltimore, even though there may not be as much of the disease here as there is in the lake regions. There, hay fever is the great summer disease, and you will often see people in the street comparing notes as to the best place to go for relief. About the first of August there is an exodus of many of the able-bodied people in town.

It is interesting to note that most of the investigations were started by people who actually suffered from hay fever. For instance, Dunbar himself was a victim, and was thus stimulated to undertake the work. His investigations opened up an important field, not only in regard to this subject, but in regard to this whole chapter of immunity. I do not know definitely, but I believe the first pollen toxin was used in Baltimore. Dunbar came here about 1903, and brought some toxin and antitoxin with him. At that time a prominent man in Baltimore was suffering from an attack of hay fever. He suffered enough to require treatment, and some pollen antitoxin was administered to him. There were no results apparent, the symptoms did not ameliorate and the question naturally arose as to whether this individual was susceptible to the kind of pollen employed in making this particular antitoxin. To solve this problem a bit of the pollen toxin was dropped upon the victim's nasal mucosa. In consequence of this he developed a violent attack of hay fever with the characteristic symptoms.

This experiment demonstrated two important facts. One was that the antitoxin was not of any particular value. That was the conclusion forced upon Dunbar, and it has since been admitted that the treatment employed in Hamburg is not very satisfactory. The other point was that there are people in this country who are susceptible to the particular pollen Dunbar was using in Germany. His experiments are extremely interesting and painstaking. For instance, the question came up as to why it is that so many individuals suffer from hay fever at particular times of the year, individuals living in the city, who do not go into the

country and do not come in contact with grasses giving off pollen to which they are susceptible. Dunbar invented a counting machine by which he estimated the amount of pollen in the atmosphere, and found that he could always obtain pollen granules in the air, even on the tops of high buildings. This brought out the practical impossibility of carrying out any effective measures to prevent the spread of pollen by elimination of particular weeds. In all districts, apparently, the pollen granules are so thickly spread in the atmosphere that individuals who are susceptible are certain to be attacked.

Investigations of this nature were especially stimulated by Ehrlich's side-chain theory, which about this time was at the height of its popularity. In that period of the development of immunology, if a man introduced a poison into an animal and obtained certain reactions, the serum of this animal afterward neutralizing the poison, it was usually admitted that we were dealing with a true toxin and antitoxin. I question if the conclusions reached by the immunologists of that period would be accepted so readily to-day as they were then. For instance, Dunbar found that animals treated with the pollen toxin produced a serum which deviated complement when brought in contact with the pollen. At the same time human beings, who were treated with the serum from the animals, showed apparently an amelioration of the hay-fever symptoms. This would hardly be accepted at the present time as the proof of true toxin and antitoxin action. Although Dunbar was at first quite convinced that horses, especially Arabian horses, produced true pollen antitoxin, this conclusion has apparently not been accepted by the majority of workers in this field. About 1902 Prof. Dunbar began a painstaking study of the vaccines against hay fever, and this work has opened up the whole subject of vaccination in this disease.

It is a difficult thing to explain the reactions which one sees in hay fever. The disease is comparatively simple clinically, as the symptoms are so characteristic that there is no doubt of the diagnosis. When we attempt to link up our theoretical knowledge of the disease with the symptoms, however, we are confronted by considerable obscurity. It is apparent that the patients show two sets of reactions at the same time. One of these we are inclined to ascribe to the condition of hypersensitiveness or anaphylaxis, whereas, the other is possibly to be explained as an immunity to the disease. It is quite evident from the work of Dr. Clowes and of others, that there are many interesting questions relating to hay fever yet to be solved.

Despite the criticism of Prof. Dunbar's work, it should be emphasized that the question as to whether he did or did not obtain a true pollen antitoxin is now of little moment. Dunbar deserves the greatest possible credit, because his work opened up the scientific study of hay fever itself, both from the clinical and the laboratory standpoint. If we compare what we have heard to-night concerning the etiology of this disease with what was taught in this school not so very many years ago, when hay fever was regarded as a neurosis, it is quite evident that science has made very definite progress in the last decade.

NOVEMBER 15, 1915.

As to the Cause of Aneurism of the Subclavian Artery in Cases of Cervical Rib. W. S. HALSTED and M. R. RED.

To appear in full in a later issue of the BULLETIN.

JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

NOVEMBER 8, 1915.

The meeting was called to order by the president, Dr. H. M. Thomas. The election of officers for the ensuing year was then held. Dr. Henry M. Hurd was elected president and Dr. Thomas R. Boggs, secretary.

Leonardo da Vinci's Anatomy. ARNOLD C. KLEBS.

To appear in full in a later issue of the BULLETIN.

NOTES ON NEW BOOKS.

A Text-Book of the Practice of Medicine. By HOBART AMORY HARE, B. Sc., M. D. Third edition, revised and enlarged. Price, \$6. (Philadelphia: Lea & Febiger, 1915.)

This new and enlarged edition of Hare's Practice is presented in an attractive format, with excellent illustrations in black and white and colored plates of varying quality.

As heretofore, the greatest value of Dr. Hare's book lies in the personal side of his experience. Especially is this noteworthy in discussions of treatment. His opinions in this field are always interesting and should teach the student to consider the reason for any therapeutic measure before ordering it. T. R. B.

The Gold-Headed Cane. By WILLIAM MACMICHAEL, M. D. With an introduction by SIR WILLIAM OSLER, B. A., M. D., F. R. S.; and a preface by FRANCIS R. PACKARD, M. D. (New York: Paul B. Hoeber, 1915.)

The original work itself needs no encomium. Everyone who has written about the Gold-Headed Cane has taken his data from Macmichael's book, and the fact that two successive editions were published in 1827 and 1828, and that it was re-edited, with additions, in 1884, by Dr. William Munk, the historian of the Royal College of Physicians, is sufficient evidence of its popularity. In the present imprint, the style and spirit of the original are preserved in a beautiful and reverent manner, the illustrations and the original title page of John Murray's second edition are admirably reproduced, and the letter-press is worthy of Murray. Sir William Osler's introduction orients us as to the purpose of the present reprint, which he regards as a fitting memorial to Radcliffe, two hundred years after his death, the present war preventing the proper ceremonials in England. He gives admirable paragraphs on the present day status of the successive owners of the cane and regards the account of Mead as the best in the volume, that of Pitcairn as the poorest. Dr. Packard follows with a clear and informing account of Macmichael, and a history and bibliography of the different editions of his book. The new title-page, which precedes the facsimile, deserves a special note. It was designed by Frederick W. Goudy, that artist-craftsman who has surpassed all others of his guild in the number and variety of beautiful fonts of his own invention. Artistic designing of types is a new departure in America, where, until Goudy took it up, we had little approaching the work of Essex House, the Vale, Dove and Ashendeane Presses, or the Eragny and Morris imprints. A native of Bloomington, Ohio, once a bookkeeper in Chicago, Goudy made his first experiment in type designing in 1896, which was immediately honored by a check from the Dickenson Type Foundry of Boston. Losing his position in 1899, he took up this special field of decorative work, and for years labored at a starvation income, having to eke out his slender resources by designing placards and other advertisements for commercial firms. But his perseverance was rewarded in time, and, after founding the Village Press in 1903, he became known to all who are interested in beautiful printing which shall at the same time be grateful to the eyes of the reader. In this he was but following his master, Nicholas Jensen, the French engraver, who was among the first to do artistic printing in the fifteenth century, and whose masterpiece, the wonderful Venetian Eusebius of 1470, is even more soothing to read than the Oporinus types of the 1555 Vesalius, or the similar triumphs of Elzevier and Simon Colinaeus. The reason is that the fonts are so cunningly conceived, the letters being founded flush with their bodies, that the curves and angles almost dovetail, yet afford an extraordinary amount of clean white space between them. Goudy has now to his credit more than thirty original fonts of these appealing letters, a record which, it is said, surpasses even the Golden Age of printing. As a gift-book of the

keepsake kind, the Gold-Headed Cane is creditable to Dr. Packard's scholarship and Mr. Hoeber's enterprise, and, as Dr. Osler says, "is an indication of the zeal with which the study of the history of medicine has been taken up by the profession of the United States." F. H. G.

Muscle Spasm and Degeneration in Intrathoracic Inflammations and Light Touch Palpation. By F. M. POTTEGER, A. M., M. D. LL. D. Cloth, \$2. (St. Louis: C. V. Mosby Company, 1915.)

A reading of this book undoubtedly makes one feel that he has in the past overlooked some interesting clinical phenomena. That muscle spasm occurs with intrathoracic inflammations is probable *a priori*, and at times is demonstrable. But the demonstration is either rare or difficult. It is to be expected that muscle spasm in the bony thoracic wall cannot be as easily detected as in the abdominal covering, and this is reason enough why we should attribute to the author, temporarily at least, a skill in technique not yet attainable by others. From our own imperfect investigations of the method, we cannot conclude that the diagnosis of intrathoracic conditions is aided thereby. But the author's observations are ingenious and will perhaps bear fruit. For his emphasis upon the serviceability of light percussion, the patients, more particularly, should be grateful. S. W.

La Tuberculose Inflammatoire. By A. PONCET, M. D., and R. LERICHE, M. D. Price, 7 francs. (Paris: Octave Doin et fils, 1912.)

According to the conception of the authors, "la tuberculose inflammatoire" is that form of tuberculosis in which the tuberculous noxus produces in the tissues merely a simple inflammatory reaction. In such a process the specific elements of the tuberculous reaction are lacking; there is no aggregation of mononuclear elements; there are no giant-cells. This non-specific reaction, the authors believe, may be elicited in any tissue, and appears under many clinical guises. The conception has already been rendered familiar to us by the work of Poncet on "tuberculous rheumatism," the atypical reaction being supposedly elicited by the tuberculous toxin and not by the tubercle bacillus itself. The argument for the wide-spread existence of such a form of tuberculosis rests upon the coincidence of unexplained inflammatory processes with definite tuberculous lesions elsewhere in the body, the two forms flaring up or quieting down together. To a certain degree the theory is attractive, but the dangerous fallacy attendant upon such argumentation arises from the great frequency of latent tuberculous lesions. It is easy to stretch the argument to the breaking-point by asserting that every human ill of hitherto unknown etiology must be an instance of "inflammatory tuberculosis" because the patient has in all probability a latent pulmonary tuberculosis or tuberculous adenitis! That the authors have succumbed to this insidious logic will be evident from a comparison of the copious index of these newly-found forms of tuberculosis with the scanty proof furnished to the eager reader. We cannot but be pleased with the wealth of interesting hypothesis; nevertheless, in most instances we remain constrained to skepticism. S. W.

Operative Surgery of the Nose, Throat and Ear. By HANAU W. LOEB, A. M., M. D. Vol. I. Cloth, \$6. (St. Louis: C. V. Mosby Company, 1915.)

This publication is to appear in two volumes. The first deals with the surgical anatomy of the nose, throat, ear, neck and larynx, and also contains very instructive chapters on the direct examination of the bronchi and œsophagus. The second volume is to be voted to the more specialized surgery of the nasal cavities, throat and larynx.

The list of collaborators includes the names of the most distinguished American laryngologists. The plan of the book is to present the subject in concise, well-illustrated articles, written by men specially qualified for the assigned topics. The section by Dr. Mosher on the examination of the larynx, bronchi and œsophagus is particularly valuable. The chapter on the surgical anatomy of the nose contains many excellent drawings made from dissections. The last hundred pages are devoted to the plastic surgery of the nose and ear. All the most satisfactory plastic operations are given in detail, and, as a rule, the various steps are shown in illustrations.

This first volume contains three hundred and ninety pages; the print is large and clear. On the whole, it is a most excellent book and should be read by everyone interested in this special line of work. S. J. C.

Reducing Weight Comfortably. The Dietetic Treatment of Obesity.

By PROF. GUSTAV GAERTNER, M. D., Vienna. Cloth, \$1.50. (Philadelphia: J. B. Lippincott Company, 1914.)

In this little book Professor Gaertner gives us in a most delightful manner the result of his long experience in the treatment of obesity. To quote his own words, he is "undertaking neither an historic presentation of the subject nor a criticism of other methods of treatment," but proposes to limit himself to a description of the methods by which he has "succeeded in reducing the weight of people living under the most different conditions."

The subject is treated in a conversational style, which makes the book a very readable and charming one. Prof. Gaertner has evidently applied common sense to his cures of obesity and has eliminated the use of the various preparations of the internal secretions, which in some of the monographs on the subject, at least, plays such an important rôle. He accomplishes his reduction cures purely by the limitation of diet, and, judging from the cases cited, he is very successful in doing so. The caloric value of the food is adjusted to the needs of each patient, and the results thus obtained are, without question, satisfactory. The weights of the diets are given in grams and Gaertner insists on the fact that every individual undergoing the treatment must weigh his food: "No scales, no cure," is his slogan.

It is a pity that in none of the cases is the caloric value of the food given. As a result of this omission, the tables lack some of the qualities that would make them of the greatest practical value. The treatment allows of any desired food, the quantity, however, being limited, while the amount of water to be taken is in no wise curtailed. These are only two of the many applications in which sound common sense has guided the author, and in regard to which there are many "fads and fancies," both among the laity and also among physicians.

Outside of the direct benefits from an obesity cure, which accrue to the individual from the point of view of vanity and greater physical well-being, Prof. Gaertner mentions certain conditions which are remarkably benefited by a reduction in weight. Thus in some of his patients he has noted a lowering of the blood pressure, the cure of certain forms of migraine, the relief of vomiting and heartburn, the disappearance of the flushes of the menopause and the correction of irregular menstruation.

Teich's Lectures on the Modern Treatment of Gonorrhœa in the Male. By P. ASCH, M. D. Translated and Annotated by FAXTON E. GARDNER, M. D. 104 pages with illustrations. Cloth, \$1. (New York: Rebman Company, 1915.)

In this book the author gives a concise résumé of the modern methods employed in the treatment of gonorrhœa by the German and French schools.

His treatment of acute gonorrhœa differs somewhat from the one usually employed in this country, inasmuch as he employs irrigations instead of injections in the early stages.

Asch uses electrargol, injected into the epididymis, for the treatment of acute epididymitis. In his hands this remedy has brought about very good results, and no impairment of function has ensued.

He prefers gonococcus vaccines to antigenococcic serum in the treatment of gonorrhœal arthritis and the various complications of gonorrhœa. His results, however, are not definitely given.

The last lecture is devoted almost entirely to urethroscopy, upon which he mainly depends for guidance in the diagnosis and treatment of chronic anterior urethritis. The pathology of the different lesions is taken up very briefly.

The annotations by the translator are valuable, in that they call attention to the various points in which the foreign methods differ from the American procedures in treating this disease.

Considered as a whole, the book is thoroughly up to date and deserves to be recommended. F. W. H.

Student's Text Book of Hygiene. By W. JAMES WILSON, M. D., D. Sc., D. P. H. Priced, \$2.50. (New York: The Rebman Company, 1915.)

In a volume of a little more than 250 pages Dr. Wilson has presented the main facts and theories of hygiene as based upon his lectures on this subject at Queen's University, Belfast. Despite the author's evident leaning to the English school of hygienists, he sees more clearly than many of his co-workers the essential distinction between the science of hygiene and the various branches of it known as Preventive Medicine, Public Health and Sanitary Science. The great influence of von Pettenkofer is not, however, clearly recognized, although the work of Pasteur, Lister and Koch is properly evaluated. The book deals with principles rather than with laboratory methods and from this standpoint is well written, concise and yet readable. The chapters on Communicable Diseases and Tropical Diseases are especially good.

W. W. F.

A Manual of the Practice of Medicine. Prepared especially for students. By A. A. STEVENS, A. M., M. D. Tenth edition. Price, \$2.50. (Philadelphia: W. B. Saunders Company, 1915.)

The fact that ten editions have appeared since 1892 is evidence of the best that the book meets a demand. If students must use a compend, Stevens' Practice is the best of its kind.

The present edition shows that the author has kept it up to date.

The sections on general symptomatology at the beginning of each system—respiratory, digestive, etc.—are very good in bringing out the possible diagnostic relations of important symptoms.

Altogether, this edition will continue the hold of its predecessors on the student body. T. R. B.

The Practitioner's Encyclopædia of Medical Treatment. Edited by W. LANGDON BROWN, M. D., F. R. C. P., and J. KEUGH MURPHY, M. C., F. R. C. S., with an introduction by SIR THOMAS CLIFFORD ALLBUTT. Price, \$8. (London: Oxford University Press, 1915.)

This book, which is a compilation of short articles by many physicians and surgeons of standing and experience, is an admirable one of its kind; it is comprehensive and fairly up to date in all the fields covered, and will form a valuable addition to the reference library of pharmacology and therapeutics.

Its large size is compensated for by the admirable lightness and clear type characteristic of the best English presses.

The first half is devoted to general and particular discussions of the methods of treatment for the diseases of the various systems. The second part takes up the agents used in treatment and contains a clear, concise and practical discussion of the different drugs and groups of drugs in the light of the most modern pharmacologic studies.

The index is excellent.

T. R. B.

Diagnostic Methods. By RALPH W. WEBSTER, M.D., PH.D., Assistant Professor of Pharmacological Therapeutics and Instructor in Medicine in Rush Medical College, University of Chicago; Director of the Chicago Clinical Laboratory. Fourth edition. Price, \$4.50 net. (Philadelphia: P. Blakiston's Son & Co., 1914.)

The fourth differs from the previous editions of this work chiefly in the addition of a consideration of many of the newer contributions to clinical diagnosis, such as methods for the estimation of the blood sugar, Lange's colloidal gold test for the cerebrospinal fluid, newer methods for staining spirochæte in tissue, etc. The sections on the Wassermann reaction and the complement deviation tests in gonorrhœa have been elaborated. In addition a new and valuable chapter on clinical bacteriology has been added. Besides the above, many other tests, the clinical value of which have not yet been fully determined, the dialysation method of Abderhalden, the Herman-Perutz modification of the Porges test and others, have been outlined. The book is well indexed, clear and concise. It has all of the features which have recommended the previous editions to students and practitioners, as well as much valuable newer material. W. A. B.

Diseases of the Bronchi, Lungs and Pleura. By FREDERICK T. LORD, M.D. 590 pages. Cloth, \$5. (Philadelphia: Lea & Febiger, 1915.)

This book is essentially a practical treatise on diseases of the respiratory organs, including the bronchi, pleura and lungs, exclusive of pulmonary tuberculosis. The author apparently realized that to include the last subject would be beyond the limits of this volume, but he has considered under various headings those conditions which might simulate pulmonary tuberculosis, and their differential diagnosis. His aim has been to formulate our present knowledge of these various diseases, as based upon a study of the literature and upon his own experience gleaned in the wards and pathological laboratories of the Massachusetts General Hospital. In dealing with various subjects included in his book a certain commendable individuality has been displayed. Though adhering in general to a well-systematized order of presentation, the author has held himself to no hard and fast rule, but has included special subject headings wherever the disease in question required it. This is perhaps best seen in his handling of lobar pneumonia. He has presented in a concise form the recent scientific advances and has included under each disease a commendable digest of those laboratory methods which may be of value in diagnosis or in treatment. Throughout the book foot-note references are given to the literature bearing upon any one subject, and so chosen as to make readily available the most important original articles. The book is well illustrated and well printed; it is singularly free from errors and makes very pleasant reading. The author has fully accomplished the aim which he had in mind, and has given us a book which will serve as an extremely valuable reference work on this subject. S. R. M.

Text-Book of Massage and Remedial Gymnastics. By L. L. DESPARD. Second Edition. Cloth, \$4.50. (London: Oxford University Press, 1914.)

In this volume the technic of Mechanical Therapeutics has been set forth in a manner which makes it somewhat difficult for the student to grasp the fundamental principles underlying these relatively simple procedures. The voluminous and unnecessary details give the reader a confusing idea of the subject and the book, therefore, to a certain extent, fails in the purpose for which it was written.

The question of "indication and contra-indication" has been treated in a "cure-all" spirit. In this respect the writer shows an unfortunate tendency very common among writers on this sub-

ject; unfortunate, because it is largely responsible for the prevalent antagonism of the medical profession toward a treatment which is of inestimable value when used in the right place and at the right time. C. R. A.

A Text-Book for Midwives. By JOHN S. FAIRBAIRN. Cloth, \$3.75. (Oxford Medical Publication, 1914.)

This addition "to the many text-books" for midwives is couched in a style which might justly awake unfavorable criticism. The subject matter is simple and for the most part well chosen; but the diction is not in accord with this commendable simplicity. There is a tendency toward the use of purely technical terms that would be staggering to the average midwife—overwhelming to the class as we know it in this country. If the English people have midwives who can read this book intelligently, they are to be congratulated. The illustrations are generally very good, but the author's choice has not been exceptionally so; many of them might have been excluded with profit and others might equally profitably have been inserted. The sequence of the subject matter leaves little to be desired and the introductory chapters on anatomy, physiology and bacteriology are excellent. The concluding chapters on venereal infection and uterine cancer are steps in the direction of public education, which should be well received.

From the standpoint of obstetrical teaching, one is rather surprised to notice the prominence given to the details of vaginal douching. At a time when the consensus of opinion is certainly against vaginal douching, *intra-partum* or *ante-partum* or *post-partum*, it would seem that the midwife should be impressed with the reasons for its avoidance rather than with numerous indications for its use. The continued reference to the many uses found for antiseptic solutions shows that the writer has not yet accurately estimated the efficiency of these drugs when used in the form of a momentary application. The occasional inaccuracies in the subject matter are presumably due to a desire not to complicate the subjects under discussion by citing well known exceptions.

E. D. PLASS.

Cancer: Its Causes and Treatment. By L. DUNCAN BULKLEY, M.D. Cloth, \$1.50. (New York: Paul B. Hoeber, 1915.)

The six lectures contained in this book show how the idea of the constitutional cause of cancer continues to exert its influence even at the present time. The author, while conceding the influence of various contributing causes in the development of the local lesion, is convinced that cancer is primarily a constitutional disease, the result of imperfect metabolism which he attributes especially to the excessive consumption of meat, tea, coffee and alcohol. So long as the true nature of cancer is unknown, every unbiased, intelligent effort to discover its cause should possess some value, but modern research and clinical observation tend to show more and more clearly that the disease is primarily a local one, and the old theory of its constitutional or humoral cause is no longer seriously considered. No new arguments in its support are offered in this work. The author, while recognizing the advances of surgery in the treatment of cancer, and also that the hope of a surgical cure depends upon early operative interference, nevertheless advocates a course of hygienic and dietetic treatment, in early as well as advanced cancer, before resorting to operation. The deplorable effect of such teaching is obvious. Its tendency to discourage operative interference, on account of the apparent hopelessness of removing what is merely the local manifestation of a general disease, and on the other hand to foster a dependence upon general remedies to cure the local lesion, until the opportunity for a radical cure is passed, is especially regrettable, in view of the educational campaign which is being carried on to enlighten the public regarding the natural history of cancer and the possibility of its operative relief. E. H.

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The Corpus Luteum of Pregnancy, as it is in Swine. By George W. Corner. With three plates. Contributions to Embryology, No. 5. 1915. 4°. 94 pages. Extracted from Publication No. 222 of the Carnegie Institution of Washington, pp. 69-94.

Diseases of the Nervous System. A Text Book of Neurology and Psychiatry. By Smith Ely Jelliffe, M. D., Ph. D., and William A. White, M. D. Illustrated with 331 engravings and 11 plates. 1915. 8°. 796 pages. Lea & Febiger, Philadelphia and New York.

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Short Talks with Young Mothers on the Management of Infants and Young Children. By Charles Gilmore Kerley, M. D. Third edition, revised and enlarged. Illustrated. 1915. 12°. 326 pages. G. P. Putnam's Sons, New York and London.

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On Pharmacotherapy and Preventive Inoculation Applied to Pneumonia in the African Native. With a Discourse on the Logical Methods which Ought to be Employed in the Evaluation of Therapeutic Agents. By Almoth E. Wright, M. D., F. R. S. 1915. 8°. 124 pages. Paul B. Hoeber, New York.

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The Practitioner's Encyclopaedia of Medical Treatment. Part I: Methods of Treatment. Part II: Agents in Treatment. Edited by W. Langdon Brown, M. D., F. R. C. P., and J. Keogh Murphy, M. C., F. R. C. S. With an introduction by Sir Thomas Clifford Allbutt, K. C. B., M. D., F. R. S. 1915. 4°. 874 pages. Henry Frowde and Hodder & Stoughton, London.

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The Nose, Throat and Ear; their Functions and Diseases. A Treatise upon the Breath-Road, Food-Road and Accessory Organs. By Ben Clark Gile, M. D. With 131 illustrations, eight of which are printed in colors. 1915. 8°. 456 pages. P. Blakiston's Son & Co., Philadelphia.

BULLETIN

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THE IDEAL OPERATION FOR ANEURISMS OF THE EXTREMITY.

REPORT OF A CASE.¹

By BERTRAM M. BERNHEIM, M.D.,

Instructor in Clinical Surgery, The Johns Hopkins University, Baltimore, Md.

Toward the end of August, 1915, Mr. W. D., aged 43, from Sydney, Nova Scotia, was referred to me by his physician, Dr. Wm. Bruce, for the relief of an aneurism of the right popliteal artery. A definite history of syphilis, practically untreated and of many years standing, was obtained and corroborated by a positive Wassermann reaction. The popliteal swelling had been present only one month, but indefinite pains of a so-called rheumatic character had been observed in the region of the knee-joint for about three months. Once the tumor had made its appearance, however, its growth had been rather rapid, and it had given rise to a considerable amount of pain, and, in addition, a disturbance in the return circulation, manifested by a gradually increasing œdema, had become apparent in the lower leg. A certain degree of varicosity was present in the veins below the knee, but the egg-sized, oblong, pulsating tumor back of the knee was obviously the prime factor in the impaired venous return.

It was hardly to be expected that an adequate collateral circulation could have developed, in view of the short duration of the aneurism, and especially in view of the fact that the dorsalis pedis and posterior tibial arteries of the foot pulsated normally. Most imperative, therefore, was a careful search to determine the state of the collateral circulation; for a definite knowledge of this feature was essential to the selection of an intelligent operative procedure.

At two independent sittings, therefore, the Moszkowicz test,² as given by Dr. Matas, of Tulane University, was carefully carried out, the result being almost totally negative. Occlusion of the popliteal artery proximal to the aneurism left a limb whose bloodless, cadaveric appearance gave mute evidence of what would occur if, in the treatment of the aneurism, some means were not found for preserving the normal arterial flow. Nor was this a case in which time could be spared for an

¹ Read before The Johns Hopkins Hospital Medical Society, October 18, 1915.

² Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries. Rudolph Matas: Jour. Am. Med. Assn., Oct. 24, 1914, Vol. LXIII.

attempt to develop a collateral circulation, since the aneurism was increasing in size somewhat rapidly, and the man was very anxious to return to his work.

On September 3, at the Union Protestant Infirmary, I exposed the aneurism, prepared to do any operation that might be indicated. A spindle-shaped tumor, as shown in Fig. 1, presented and was opened on its dorsal aspect, revealing only two openings, the entrance and exit (Fig. 2) of the popliteal artery, the two points being distant about an inch and a half from one another, and only the faintest sign of a groove being apparent between them. The popliteal vein was so densely adherent to the sac that it was impossible to separate it without taking part of the sac wall, which, of course, was done.

To have attempted a reconstructive Matas endoaneurismorrhaphy under the circumstances would have amounted to little more than courting disaster. Hence, keeping in mind the insufficient collateral circulation, without further ado I removed about 15 cm. of the internal saphenous vein from the affected leg at the knee and, after proper preparation, interpolated³ about 12 cm. of it between the severed ends of the popliteal artery. Only the ends of the sac were cut away (Fig. 3), the remainder being left to be folded around the transplant as a partial reinforcement (Fig. 4). Carrel's end-to-end suture was used, and the distal end was united to the graft first, because the artery was most deeply situated at that point. It is worthy of note that the wall of the artery was thicker than normal, had numerous pin-head-sized dull-gray plaques in its intima and was so friable that it tore badly in its preparation for suture, rendering necessary the removal of an additional centimeter and a half from the distal end. The suturing itself was accomplished without great difficulty, and at its conclusion blood went through the graft in a normal manner, except for the presence of the marked dilatation so graphically illustrated in Fig. 4.⁴ The dorsalis pedis and posterior pulses could be felt at once and remained normally palpable at all times. An uninterrupted convalescence ensued and the patient returned home not only able to walk well but also, as he himself volunteered, "able to get on his shoe with a sock on his foot," whereas, prior to operation, this had been impossible owing to the oedema. All pain and discomfort in the leg had disappeared and a curious preoperative "dead feeling" of the great toe had given way to a normal feeling. Pulsation could be felt all along the vein graft as well as in the arteries of the foot.

So far as I have been able to determine, no case similar to

³ The vein segment was "reversed" so that its valves faced the foot instead of the heart, as they normally do. This is a most important step in every venous transplant, since the arterial current will be forced to break down the valves, unless they are reversed.

⁴ It is hardly necessary to add that this dilatation is really a "normal" occurrence in every instance in which a vein is subjected to arterial pressure. The vein wall is thinner and has less muscle tissue than the arterial wall, and it therefore gives. Later on it hypertrophies and undergoes a fibrous change, which enables it to withstand continued arterial pressure without difficulty.

this⁵ has been reported from this country, and hardly more than seven from elsewhere⁶—a rarity that is most discouraging to those who had hoped for real practical developments in modern vascular surgery.⁷ Perhaps other cases will be dealt with in a similar way, as the intelligent study of vascular conditions in general and of aneurisms in particular becomes more widespread. Many limbs have been sacrificed because a definite knowledge of the state of the collateral circulation was wanting at the time of operation. Dr. Matas, whose work in the field of aneurisms has brought him such well-deserved renown, has emphasized this point in numerous papers; and the case just cited is an eloquent proof of the necessity for this determination prior to operative interference. Many difficulties will be encountered in carrying out the tests, and they are not without a certain amount of danger; hence, they will probably have to be modified. Nevertheless, be that as it may, the knowledge is essential and must be had at all costs.

DISCUSSION.

DR. HALSTED: Dr. Bernheim is to be greatly congratulated. The indications for the transplantation seem to have been clear, and the operation was a complete success. It is well termed the "ideal operation," when the indications for transplantation are so definite as they were in the case just reported by Dr. Bernheim.

We are indebted to Alexis Carrel for making such an operation possible. Prof. Lexer, the distinguished director of the surgical clinic of the University of Jena, is responsible for the term, and he was probably the first to transplant a blood vessel in the treatment of aneurism. Many surgical procedures have been called "ideal" and for their time have, perhaps, deserved the appellation. Most of them were, however, short-lived. Some surgeons, myself⁸ in the number, have advocated excision of the aneurism under certain conditions. By Bramann and by Delbet excision was termed the "ideal operation." Lexer reported his first case at a meeting of the Deutsche Gesellschaft für Chirurgie eight or nine years ago. The operation was for an aneurism in the axilla, the result of an attempt by some surgeon to reduce an old dislocation of the shoulder-joint. The operation was successful so far as concerned the patency of the vessels; but the patient died in a few days of delirium tremens.

Four or five years later Lexer reported a second case, also successful. In this a long piece of the saphenous vein was transplanted into the defect caused by the excision of a popliteal aneurism. Lexer has performed his "ideal operation" in a third case, the details of which I cannot at this moment recall. In several other instances in the human subject the transplantation of a vein to replace an arterial defect has been undertaken, usually with unsuccessful result. The surgeon who attempts this operation

⁵ The first operation of this kind was performed in 1906, by Lexer, who was then in Jena. In a paper appearing in the Arch. f. klin. Chir., 1907, lxxxiii, 458, he spoke of the procedure as "The Ideal Operation for Aneurisms," and it has gone by this name ever since.

⁶ Abalos, J. B.: (Fusiform popliteal aneurism; extirpation, circular suture; reestablishment of normal circulation.) Spitalul. Bucuresci, 1914, xxxiv, 183-191.

⁷ Surgery of the Vascular System. B. M. Bernheim. J. B. Lippincott Co., Phila., 1913.

⁸ Ligation of the first portion of the left subclavian artery and excision of a subclavio-axillary aneurism. Johns Hopkins Hospital Bulletin, 1892, Vol. III, p. 93.

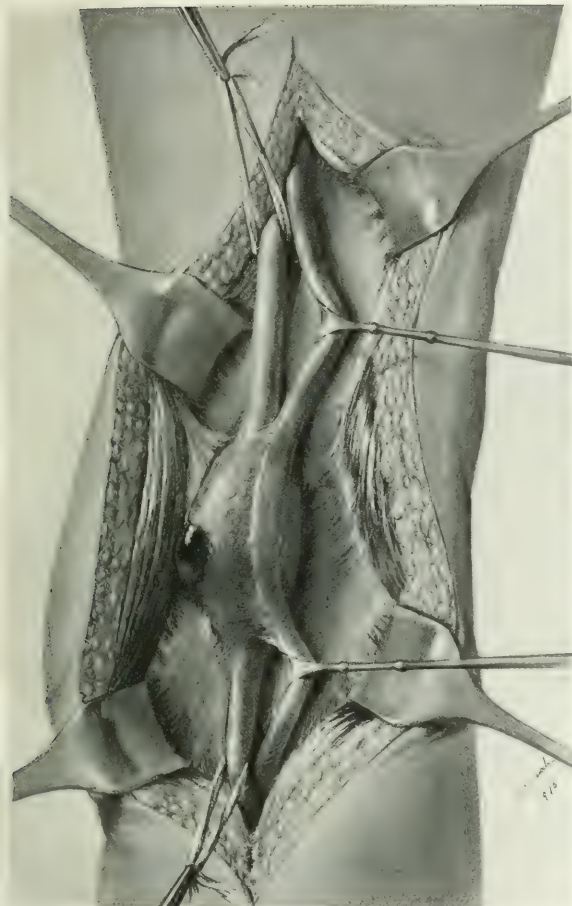


FIG. 1.—The aneurism and the accompanying vein are exposed, showing dense adherence of the vein to the sac-wall. The small dark bulging area in the sac-wall was the site of a threatened rupture of the sac, evidently caused by manipulations during the application of the Moszkowicz test.

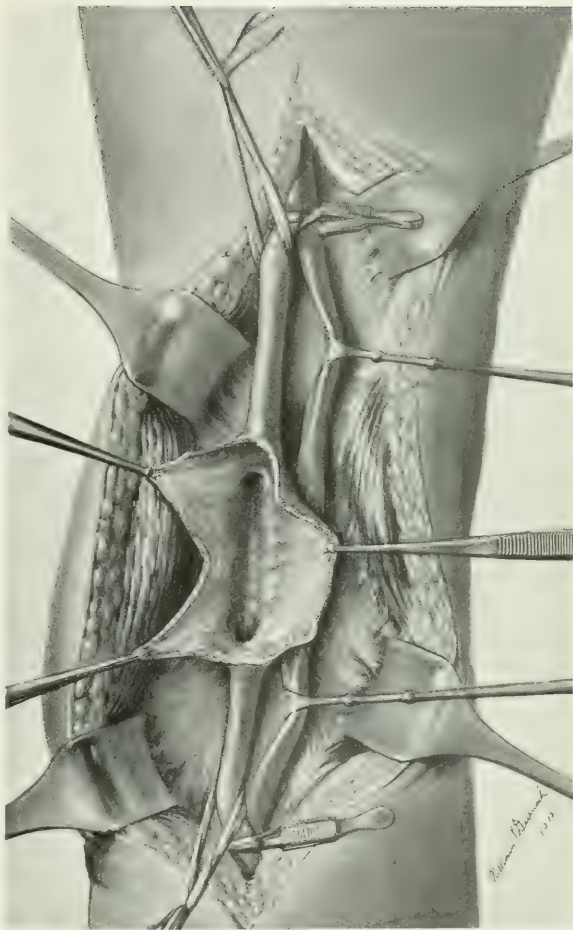


FIG. 2.—The aneurismal sac opened, showing the entrance and exit of the popliteal artery. The drawing greatly exaggerates the groove between these points.

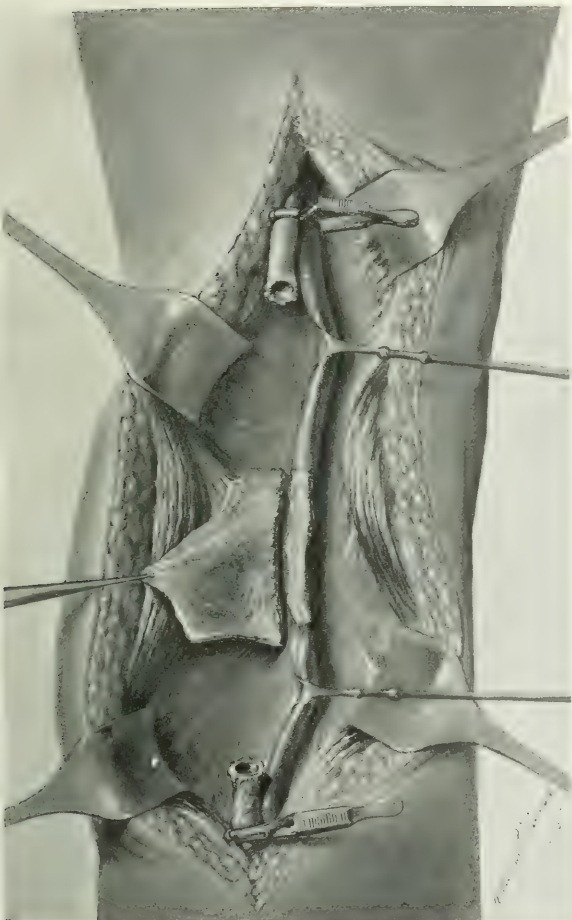


FIG. 3.—The aneurismal sac cut away from the popliteal artery. The vein was separated from the arterial sac by taking part of the sac-wall with it. With the exception of the ends of the sac, all the remaining portion was left *in situ*. The ends interfered with the placing of the venous graft.

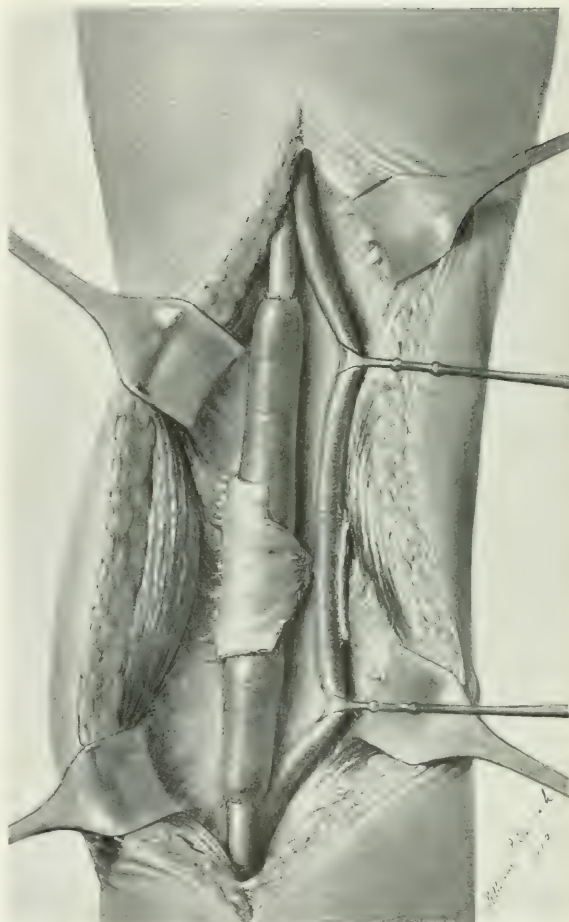


FIG. 4.—The vein graft has been sutured to the ends of the popliteal artery and the aneurismal sac wrapped around it for the purpose of reinforcement.

without having practised it on animals will almost surely fail to accomplish it successfully.

Six years ago I invited Dr. Bernheim to transplant for me a long piece (12 to 14 cm.) of the saphenous vein into an arterial defect caused by the excision of a sarcoma of the popliteal space. In this case the popliteal vein, the internal popliteal nerve and the popliteal artery, from Hunter's canal almost to its bifurcation into the tibials, had been excised. The vascular suture at the lower end of the space was quite difficult on account of the depth of the wound and the relatively small size of the distal stump of the artery. For a time the circulation through the transplant was perfect, but the interpolated vein became thrombosed* before the wound could be closed. Gangrene did not, however, ensue.

I might mention in this connection that an end-to-end suture of the aorta has been successfully accomplished. In excising a retroperitoneal tumor, Braun tore into the abdominal aorta and after excising about 2 cm. of this artery was able to sew the widely separated ends together.

Prof. Kummel, of Hamburg, told me of a recent interesting experience of his own. On excising a tumor he made a hole in the abdominal aorta. This he closed with a suture of coarse silk and, if I remember correctly, without the use of oil or vaseline. A second uninterrupted suture of fine silk was taken to reinforce the first.

I should like to be the first to call attention to a possible flaw in my argument for practising the partial occlusion of an artery in the treatment of certain cases of aneurism. As some of you perhaps know, I advocate the employment of a band which can readily be removed and which does not injure the wall of the artery, in order to test and then to encourage the anastomotic circulation. But I realize that it may be possible, even with only partial occlusion, to interrupt the blood flow totally and too quickly. Thus, following the application of a band which still permits a small stream to flow through the artery to the aneurism, the latter might so promptly become solidified by the clotting of its contents that gangrene would be threatened. It is obvious that in such a case removal or loosening of the band might not restore the circulation through the aneurism.

My own experience with vascular suture in the human subject has extended only to veins and to the lateral suture of a defect of the femoral artery in Hunter's canal.

Of particular interest to me is the case of a patient upon whom, with the assistance of Dr. Heuer, I operated four or five years ago. We had about completed the removal of a very large lymphangiomatous cyst of the abdomen. There remained to be freed only its connections with the inferior vena cava. While these were being separated with extreme caution, blood gushed from this vein. There proved to be a linear defect in the vena cava so long that six artery clamps were required to close it. A lateral suture of the vessel with oiled, fine silk was successfully accomplished. The patient's convalescence was uneventful and she is at the present time in excellent health. The defect in the wall of the vein was not an artefact. It represented, I believe, an imperfectly

closed orifice from the vein to a lymph-bud or lymphatic vessel from which the cyst had had its origin. I expect to report, later, this case and an analogous one, in detail, because they may serve to account for the occasional presence, hitherto unexplained, of blood in certain lymphangiomatous cysts, and for the observations that cysts which on the first tapping yielded a clear fluid have, on subsequent tapplings, been found to contain more or less blood.

Thus Professor Jordan and Professor Voelcker,¹⁰ of Heidelberg, refer to a case of cyst of the neck, reported by Weil, which had its origin, he believed, in a hemorrhage from the vascular wall of a cystic lymphangioma. In support of Weil's view, the authors instance the observations, repeatedly made, that cysts from which at the first puncture only a clear serous fluid was withdrawn at subsequent aspirations sometimes yielded blood. And one frequently meets with the statement that the serous content of lymphangiomatous cysts may *after injury* become bloody.

As a possible explanation of the occasional presence of blood in lymphangiomatous cysts I would suggest that a primordial communication between the vein and the lymphatic cyst may not have been completely closed. The presence of blood, at subsequent aspirations, in the content of cysts, which at the first tapping had yielded only a clear serum, might be due to the relief of tension in the cyst rather than to an injury of its wall; for the pressure within the cyst being diminished or negated, there might be a retrograde flow of blood from the original venous connection.

In one of my cases, a supraclavicular hygroma, a definite relation to a large vein of the neck was demonstrated, and in the other, as I have related, there was an intimate connection with the inferior vena cava and evidence of an opening between the cyst and the vein which may have become closed more or less completely by a cribriform fascia of some sort. It is, I believe, very improbable that the thin non-vascular walls of either of these lymphangiomatous cysts could have contributed much, if indeed any, blood to their contents; and to continuously furnish blood enough to stain the fluid for possible frequent subsequent tapplings would, it seems to me, have been, for such walls, impossible.

DR. BERNHEIM: It had not occurred to me to do the Moskowicz test on the other leg, as suggested by Dr. Halsted. We had trouble enough doing it on the one. It seemed quite painful and, to tell the truth, I thought it not devoid of danger. We used a small roll of gauze about 2 inches wide, one end of which was made into the shape of a cone, so as to facilitate the making of pressure between the big muscles just above the knee. With this in the palm of my hand, I clamped down on the artery above the aneurism, but the vein must have been shut off at the same time. I realize that an instrument has certain advantages over the hand in making this pressure, but it also has disadvantages that, to my mind, outweigh the advantages. Any one who has attempted to get the popliteal pulse, and has had the usual difficulty in locating and palpating it accurately, will realize the amount of force necessary to occlude it. This in itself is, perhaps, not so terrible, but one can never be sure that an offshoot of the aneurism is not caught under the pad. Hence I have about decided not to use the test in that form any more. It would seem far more conclusive to make an incision above the aneurism and apply a band which will occlude the artery entirely—but only the artery. With a dressing in place over the small wound, the collateral circulation could be determined with positive accuracy and with great promptness; and, best of all, such a procedure would be entirely devoid of danger. At its conclusion the operative procedure indicated could be carried out with a sense of comfort and confidence that is not felt at present.

*The most serious objection to the "ideal" or veingrafting operation is perhaps this: that in case of failure the thrombosis which starts in the graft may extend either centrally or peripherally, or in both directions, from the interpolated vein into the artery and thus involve important anastomotic branches which would not have been threatened with occlusion if the artery had been merely ligated, or the sac merely excised or plicated. The transplanted vein is, consequently, a menace, for in at least two-thirds of the cases in which the "ideal operation" has been practiced, thrombosis has occurred in the insert.

¹⁰ Handbuch der praktischen Chirurgie, Bd. II., S. 117.

MEMORIAL MEETING TO DR. E. L. TRUDEAU.*

THE LAENNEC.

DR. JANEWAY: Since the Laennec Society last met here a famous figure in the field of tuberculosis study has passed away—Dr. E. L. Trudeau. Not only was Dr. Trudeau the most famous pioneer of tuberculosis investigation and treatment in America, but he was in a very particular way the hero of all of us physicians in this country throughout a long life.

In the year in which I was born, Dr. Trudeau, then looking forward to a highly promising career in medicine in New York City, came into my father's office and was told by him that he had very definite signs of tuberculosis of the lungs, and his career seemed, in all human probability, a failure. How different he made it! From that time on, whenever I would become discouraged with the way things were going with me, my father would take occasion to point out to me what Dr. Trudeau had accomplished from an apparently hopeless outlook. Nothing was much more hopeless at that period than the outlook for a physician with tuberculosis; but his career has been one of the most brilliant in the history of American medicine, and one of the most fruitful, both in the quality of his scientific achievement and in what he accomplished for sick men and women.

Dr. Trudeau was not himself a Hopkins man, indeed he could not have been, for the Hopkins Medical School did not exist at that time, but he sent his two sons here; and while we are all hero-worshippers (everyone worth his salt is, and especially every physician) I have come to believe that Hopkins men are particularly hero-worshippers of the right sort of medical heroes. So it seems especially fitting that this first meeting of the Laennec Society for the year should be given over to an attempt to bring before those of us who had the privilege of knowing Dr. Trudeau, and to many of you who only knew him by reputation, the achievements, and still more, the characteristics which marked his career and which are such a stimulating example to every one of us.

We had hoped that Dr. Welch might be here and speak from the fullness of his personal knowledge and appreciation of Dr. Trudeau's scientific work, but a meeting of the China Medical Board, which it was imperative he should attend, was called for to-day. We are, however, exceedingly fortunate in having with us three men who knew Dr. Trudeau intimately; one his senior pupil, as it were, and all three his personal friends, who will speak to us on the different aspects of Dr. Trudeau's life and character, so far as it is possible to separate the different aspects from one another. That any of them can think of Dr. Trudeau other than as the man, is impossible, but each will try to tell us something of that side of Dr. Trudeau which is set opposite his name on this evening's program. Of course, if Dr. Osler were here, he would have spoken of Dr. Trudeau with that enthusiasm and insight which we all know how to expect from him. Though absent, he still is with us to-night in spirit, and has sent us a cablegram which I will read to you:

Through failure to success, Trudeau passes among the elect. Human sympathy and unfailing optimism made him a strong defense to the stricken. The noble example of his life will remain a permanent inspiration in our profession.

OSLER.

Dr. Walter B. James, of New York, will speak to us of Dr. Trudeau, the physician.

DR. TRUDEAU, THE PHYSICIAN.

BY WALTER B. JAMES.

It is fitting that this memorial meeting should be held in Baltimore, for Dr. Trudeau cherished a warm affection for The Johns Hopkins, and turned to it for help in some of his periods of greatest suffering, and he knew that nowhere was he more sincerely loved than here, and nowhere was his work more appreciated. It is fitting, too, that it should be at a meeting of the Laennec Society, for Trudeau and Laennec had much in common.

They both possessed the Gallic temperament and the power to be cheerful under overwhelming vicissitudes, and so, like their nation to-day, snatch victory from defeat. Both were subjects of the very disease that was their life study, and to which they made numerous and valuable contributions, and each, a devout Christian, awaited, with fortitude and without complaint, the coming of the end whose signs he knew only too well.

The brief and impressive document to which each member of our profession must assent before he may enter upon its practice, in spite of its antiquity and its archaic phrases, is still the best epitome of the duties of the true physician; and the Hippocratic oath remains the standard for the conduct of the medical life. To treat the sick with no thought for himself, but with every thought for them, and with honesty and truth to teach to those who follow him all the knowledge he has acquired.

Had the vague yearnings of mankind to know the nature and origin of the maladies that plague them at that time crystallized into the activities that we know now as medical research, this, too, would doubtless have been included in the oath.

This document breathes in its every phrase the highest spirit of medicine and, tested by it, Dr. Trudeau's life stands out as a splendid model for the physician.

It is 36 years ago this coming summer that I first heard of him. I had gone to the Adirondacks, to Blue Mountain Lake, to recuperate from the effects of a winter of too great enthusiasm for biology under the stimulating influence of your Newell Martin.

The Adirondacks was a wild region compared to what it is at present, but rumors reached me of a young doctor whose fame was widespread in the northern district, 70 or 80 miles away. I heard nothing of his professional renown but only that he was a splendid hunter and a remarkable shot with the rifle.

Laennec, too, was a sportsman, and it is related of him that his friends accused him of taking more pride in his horsemanship than in his professional achievements.

* Proceedings of the Laennec Society, January 24, 1916.

A few years later it was generally admitted by us all in the laboratories of New York and elsewhere, that the only man from whom a trustworthy and pure culture of tubercle bacillus could be obtained was Dr. Trudeau. Then we heard that he had built a small sanatorium on a novel plan; soon, that he was one of the best men in the country to whom to send cases of early tuberculosis.

Not long after, I met him for the first time at Paul Smith's, when on a summer trip through the woods, and I was at once impressed by his tall, straight, alert frame, his keen and responsive interest and the sweetness of his smile. By that time he had begun to be famous throughout the world as a physician. This was the beginning of one of the most cherished friendships of my life.

The exigencies of this evening's program separate the achievements of the physician from those of the investigator and the man, but I suspect that in few men have these three activities been more closely tied together. His professional life was spent in a little village in the woods where distractions and amusements were few and of the simplest and most natural kind. His real friends were his patients, and they paid him occasional visits in the morning for professional advice, then came to spend evening after evening in his cheery library throughout the long winters, a little company closely knit together by the ties of isolation and common misfortune, but a company, than which one will rarely find one more light-hearted and gay.

His experimental laboratory, too, at first in his house, was later a structure so closely adjacent to it that the visitor, from his bedroom window, looked across a few feet of deep snow to the sturdy stone building where the experiments on immunity and resistance were being carried on.

There were no fixed hours for work or for rest, and even the examining office and dispensary of the sanatorium were in his own home. Thus his practice, his hospital and his laboratory were part of his daily life, and inseparable from it, and he never bore well a longer absence from them than one or two weeks.

I first heard from him a quotation which, we used to agree, briefly but comprehensively described the ideal aim of a physician. "*Guérir quelque fois, soulager souvent, consoler toujours.*" and this describes not only his aim but what he made his own life express.

He would have been a distinguished and successful physician under any circumstances and in any circle, for he had the fundamental intellectual qualities that make for success in our profession. He had unusual diagnostic acumen, for he had the faculty of brushing aside or ignoring the little things that so often lead the mind of the unwary clinician from the straight road to truth, and, with an instinct that often seemed like a woman's, he would arrive at a correct diagnosis by means that were not easy to follow.

A skeptical stranger once presented himself to him for examination and the doctor found the chest painted with iodine over the right lung apex. After careful search he discovered signs of very slight phthisis in the left apex. He then

asked the patient why he had painted the sound side; "To see if you would know" was the reply—a device that might well have tripped a less experienced and wary examiner. He told me this tale with keen enjoyment, for his sense of humor was exceptionally well developed, and stood him in good stead on many occasions of sore trial. A sense of humor seems a necessary part of the equipment of the complete physician.

When we think of how his life was passed in the woods, surrounded by cases of one single disease, his attention focused upon this with singular intensity, for he engaged in but little general practice, it is remarkable that he so rarely erred, and confounded other conditions with tuberculosis. He was especially happy and successful in his relation to that always puzzling group of cases, where lassitude and slight loss of weight with perhaps rapidity of the pulse are the only symptoms that suggest in young people possible tubercular trouble in the lungs; and he rarely erred.

His invaluable contributions to the rest and fresh air treatment of tuberculosis I shall not describe, for these will be spoken of to-night by one whose relations to Dr. Trudeau's work were even closer than mine, but I should like to say a word about one phase of his therapeutic achievements that belongs to his life as a practicing physician.

Every doctor is conscious at times of a feeling of disappointment, even of resentment, when advice which is founded upon the principles of modern scientific medicine is unheeded by the patient, and we are generally human enough to ascribe it to the vagaries of the individual, rather than to our own delinquencies.

When one has viewed the work of one like Dr. Trudeau from close at hand as I have done, and has marveled at his ability to secure the conscientious performance of every therapeutic duty prescribed, exposure hour after hour to cold, the tedium of months spent at absolute rest in bed, with a prescribed diet, one wonders what quality it could be that the man possessed enabling him to so override objections and secure the cooperation of his patients. Was it not that indefinable quality which some men have of carrying conviction by simple words, of impelling belief in the wisdom of counsel, of inspiring confidence through singleness of devotion to their patients' interest? A quality of inestimable value to a doctor.

The duty of the physician does not stop with the writing of a wise prescription or the giving of advice, and it is the one who can secure the carrying out of his counsels who fills the full measure of his responsibilities. Many of Trudeau's clinical victories resulted from this ability to secure the complete out-of-door rest cure for the patients who had refused such measures until they fell into his hands.

His unworldliness and his forgetfulness of self were nowhere more in evidence than in his relation to the very poor, who soon flocked to Saranac Lake with a hopefulness that was pathetic.

Trudeau was a born teacher. He had the spirit of Erasmus. It was not many months after the establishment of his little home-made laboratory in his house at Saranac Lake before men began coming to him to learn how to culture the tubercle

bacillus, how to isolate it and, above all, how to design sanatoria and carry out the principles of out-door treatment.

I can remember that during the years when he was enjoying a fair measure of physical vigor, and was able to come to New York once or twice in the winter for 10 days or two weeks at a time, it was always understood between us that he should give one of my clinics at the college, or possibly a lecture, and during those years I made it a point that every one of my classes should have the opportunity of hearing his views on the early diagnosis and treatment of tuberculosis; and he was never happier than on these occasions.

In his autobiography he tells how a doctor brought, all the way from Australia to Saranac Lake, a young man with tuberculosis, because he himself had heard Trudeau describe the out-door cure and its result on one of the above occasions. Later his voice became so thin that he could be heard only with difficulty in the lecture room, and, to my sorrow and his, he was reluctantly compelled to give up this annual function.

The Hippocratic injunction to teach was one that he obeyed throughout his entire working life, and Saranac Lake became a Mecca for those in search of information regarding tuberculosis. The sanatorium that he founded and in which he took so much pride soon became a model for such institutions.

The most striking and stimulating phase of his teaching activity was his influence upon young physicians who came to him disabled by the disease. It was an occurrence pathetically frequent for medical students or recent graduates to come to me with the familiar story of a slight hemorrhage, or afternoon fever, or a few tubercle bacilli found in the sputum, always downcast and discouraged, and with a feeling that their professional career was at an end. Generally I had little difficulty in cheering them up when I gave them an account of Trudeau, what he had accomplished and what other men in their situation had succeeded in doing in spite of these obstacles; and I would send them to Saranac with a letter to him and with advice to put themselves entirely in his hands, for I knew what the result would be; a few weeks or a few months, perhaps even a year, spent on an open porch, later with an electric light over the couch where, presently, medical literature, especially the literature of tuberculosis, would be studied; then, with the absence of fever and the return, in some measure, of physical vigor, an opportunity to do a few hours' or a half day's work in the laboratory, and so the establishment of an interest that would last for the rest of their lives and leave them further advanced in their profession at the end of their cure than they would have been had they pursued their original course of life.

Many of the most useful and productive workers in the field of tuberculosis, now scattered throughout this country and Canada, are "graduates of Saranac," who there, under Trudeau, found health and at the same time opportunity and encouragement to enter upon a life of research.

I have never known Dr. Trudeau's front door in Saranac Lake to be locked, and every evening for many, many years in his cosy library there was an informal gathering of the younger and older doctors, who sat at his feet, and the discussion was almost always of matters in some way related to

the disease that had brought them there. These gatherings, in which I have from time to time enjoyed the privilege of taking part, constituted a school in the truest sense, and a school that reminds one of what we read in the history of the early days of learning.

His patience in listening to his pupils, his kindness and complete absence of arrogance, the freedom with which he gave to everyone all that he knew—these qualities, together with the indefinable charm that drew these young men to him, made him a great teacher. Just as an interest in the study of tuberculosis had been of inestimable value to him in stimulating his own recovery, so I am sure did he lead many a young doctor back to health, through the development of a similar interest.

It is a fundamental law of nature that effort is stimulated by resistance, and in some of the recent results of the comparatively new science of anthropogeography, I am often reminded of Trudeau and what I believe his environment did for him. As Huntington shows that in factories the workers put forth their maximum production in periods of greatest climatic rigor, and when he shows that the degree of civilization in Europe now and in the past coincides with areas of maximum climatic storminess, it tempts one to the stimulating and encouraging thought, that perhaps the storminess of Trudeau's fate acting upon his strong nature helped to produce the unusual result that we are celebrating to-night.

As the direct result of his splendid medical life he has left behind him in Saranac Lake a group of institutions that will endure—a sanatorium that is a model for all the world, teaching how cases of early tuberculosis should be managed, with productive research laboratories maintaining high ideals of work and especially utilizing the skill and intelligence of physicians while they are completing their recovery.

But, best of all, he has left a spirit which animates all medical life that is worth while, and which is the soul of modern medical science; research for the sake of practice, and practice for the sake of humanity.

The value of such a life as Trudeau's to our profession cannot be estimated. For many years an influence has radiated from the village in the woods stimulating men to a fuller and more perfect carrying out of its fundamental precepts. But as matter is indestructible and as force is indestructible, so the power of such a life as his is imperishable. It will go on year after year, helping generation after generation of men to practice medicine better because he lived so complete and so perfect a medical life, even though in so remote a spot.

"So be my passing!

My task accomplished and the long day done,

My wages taken, and in my heart some late lark singing,

Let me be gathered to the quiet West,

The sundown splendid and serene."

DR. JANEWAY: Dr. James has told us something of the school which gradually grew up around Dr. Trudeau at Saranac Lake, one of the few really distinctive American schools in medicine.

There has come to us to-night from Saranac Lake the oldest pupil of that school, a pupil upon whom the headship must

fall, now that Dr. Trudeau has gone; the man to whom we in this country look for the most authoritative opinion both upon the clinical problems of tuberculosis and those complex and still unsolved problems of immunity to it. Dr. Baldwin, of Saranac Lake, will speak to us on Dr. Trudeau, the investigator.

DR. TRUDEAU, THE INVESTIGATOR.

BY DR. E. R. BALDWIN.

It is 15 years since Dr. Trudeau himself gave a reminiscent talk before this society on the history of his experimental work. It is most gracious of your president to grant me the privilege of reviving the memory of that account. It was a story of an extraordinary effort by an extraordinary man. Those now present who listened to him will readily recall his dramatic description of the home-made incubator box. He always spoke humorously of the bacilli freezing and thawing, but was very proud of his achievement in growing the tubercle bacillus so early with his primitive apparatus. He was, in truth, a pioneer in a field little touched by those not directly concerned with tuberculosis. By that I mean those who never had it themselves. No description that I can give will compare with his earnest, entertaining style in relating his early difficulties and experiments. I cannot refrain from quoting his own words found in his autobiography just published (Chapter XVI, pp. 201-203):

In the fall of 1885, as soon as I had equipped my little laboratory room, I began to work. At first my knowledge was limited to the detection of the tubercle bacillus in the secretions of patients, and my observations to verifying Koch's claim that this bacillus was the cause of the disease and was always found when tuberculosis was present. I made examinations of all my cases, and as a result found only one patient in whom, while the symptoms of consumption of the lungs were present, I could never detect the bacillus. I made a study of this case and proved that it could not be tuberculosis, as the expectoration would not kill animals, while the expectorated matter which contained tubercle bacilli always produced generalized tuberculosis in the guinea-pigs. I published this study under the title of "An Experimental Research upon the Infectiousness of Non-bacillary Phthisis," in the *American Journal of the Medical Sciences* for October, 1885, and this was my first publication from my little laboratory room. I am afraid I have been guilty of many others since!

The thing I craved to do, however, was to succeed in cultivating the tubercle bacillus outside of the body and then produce the disease with it in animals. It was the early winter of 1885 when I attacked this problem with great earnestness. I had learned from Dr. Prudden how to make artificial media—beef gelatin, beef agar and other media—but the first growth of the tubercle bacillus direct from animal tissue I knew could be obtained only on solidified blood serum, and then with difficulty. I bought a small sheep for three dollars and a half, and from the sacrifice of this animal I procured the required amount of blood, which, thanks to the pure air and the snow upon the ground, remained tolerably free from contamination and was transferred at once to the ice-box to coagulate. I am afraid my associates at the laboratory to-day would hardly consider the technique I then employed up-to-date, but after many incidents I succeeded in getting some fair plants of blood serum in tubes.

I made plants on this blood serum from a tuberculous gland removed from one of my inoculated guinea-pigs, and put all the tubes in my home-made thermostat. For the next two weeks I watched the temperature of my absurd little oven with jealous

care, and I remember one very cold night getting up in the night and going down stairs to look at the temperature. Many of the tubes turned out at once to be contaminated and a variety of growths appeared on them; but after ten days I still had four tubes free from contamination, and these looked much as when I first put them in the incubator. On the eighteenth day I thought I detected a little growth in the corner of one of these. With every precaution against contamination, with my platinum spade I removed a little of the suspected growth and rubbed it on a couple of clean slides, dried it and stained it. My first intimation of success was when one or two large masses on the slide refused to decolorize when treated with the acid. I washed the slide, put it under the microscope, and to my intense joy I saw nothing but well-stained culture masses and a few detached tubercle bacilli. I at once planted some fresh tubes from the one I had examined, and I knew now I had pure cultures to work with. This little scum on the serum was consumption in a tangible form. With it I could inoculate animals and try experiments to destroy the germ. (An Autobiography, Dr. E. L. Trudeau, pp. 201-203.)

After mastering the culture of the bacillus he naturally made efforts to show the actual effect of therapeutic agents on it. This perfectly obvious and rational procedure, as a prerequisite to the employment of supposed germicidal treatment, indicates that the 10 years of wilderness life had not dulled his intellectual gifts. To quote his own words (Autobiography, p. 204):

As soon as I had pure cultures I began to inoculate rabbits and guinea-pigs, and started some experiments to try to kill the germ in their tissues by the injection of various germicides, such as creosote, carbolic acid, and other substances known to destroy germs. These experiments of mine all failed, and I found, as I expressed it to the students one day at the College, that "the tubercle bacillus bore cheerfully a degree of medication which proved fatal to its host!"

He also tried hydrogen sulphide and hydrofluoric acid gas, the latter forming the subject of his third contribution in print. Later (1888), he published clinical experiments with hot-air inhalations, the conclusions from which were so logical and well-stated as to give an index of his good reasoning faculties and clearness of expression. His summary is as follows:

First, the therapeutic value of hot-air inhalations in phthisis is doubtful. Second, the evidence obtained by the bacteriological study of the cases does not confirm the assumption that inhalations of heated air can either prevent the growth of the tubercle bacillus in the lungs of living individuals or diminish the virulence of this microbe when it has gained access to them. (Trans. Assn. Am. Phys., 1889, Vol. IV, p. 291.)

The work that probably attracted most attention to Dr. Trudeau as a scientist was the so-called Environment Experiment which he did in 1886 and repeated in 1887. I refer to the really simple but brilliantly executed experiment whereby he demonstrated on rabbits three very important truths.

The first one was that confinement, bad air, and restricted food without the bacillus could not produce tuberculosis. The second, that the conditions just described plus inoculation with tubercle bacilli led as a rule to a fatal infection. Finally, rabbits similarly inoculated and turned loose on a little island near his summer camp, recovered; in fact, he had to shoot them to catch them! It must have been a great encouragement to him, and it has rarely happened that a therapeutic

experiment has received such a widespread demonstration of its value during the lifetime of the author.

Here is his own description of the confidence it gave him:

This showed me conclusively that bad surroundings of themselves could not produce tuberculosis, and when once the germs had gained access to the body, the course of the disease was greatly influenced by a favorable or an unfavorable environment. The essence of sanatorium treatment was a favorable environment so far as climate, fresh air, food, and the regulation of the patient's habits were concerned, and I felt greatly encouraged as to the soundness of the method of treatment the sanitarium represented, even though it did not aim directly at the destruction of the germ. (pp. 204-206.)

The simplicity of this experiment and the novelty of its application made a strong appeal to his friends both lay and medical. I well remember the story of this experiment related to me when a medical student.

During each of the succeeding years until 1896 Dr. Trudeau was able to present some reports of experimental work from his laboratory. The most interesting of his contributions, and the most important, were his experiments with tuberculin. Influenced by the published work of Pasteur on protective inoculations he had engaged in much the same line of experiments simultaneously with Koch. His results were unfavorable and were published on November 22, 1890, shortly after the premature announcement of tuberculin as a cure by Koch in August of the same year. Dr. Trudeau obtained, nevertheless, prolongation of life in his treated guinea-pigs, and from that time until his death held to his faith in the possibilities of tuberculin and other specific vaccines. It must be conceded that this buoyant hopefulness was succeeded by skepticism in his periods of depression, but it was always founded on faith in his observations on animals. Before the discovery of tuberculin I found a short note of his in the Transactions of the Association of American Physicians, in May, 1890, when, in discussing one of the papers on tuberculosis, he indicated his faith in Pasteur's work. He said:

I think, perhaps, Dr. Shakespeare has not presented the most encouraging side of Pasteur's work. Pasteur has not only taught us that anthrax and chicken cholera are due to a germ, and that hydrophobia is caused by a specific virus which has its seat in the spinal cord, but he has taught us as well that by his methods these diseases are now already somewhat under control of man, and can be prevented to a great extent. We need not, therefore, necessarily take too gloomy a view so far as tuberculosis is concerned.

This faith was maintained throughout the quarter-century of life that remained to him. As evidence I will read a letter written last summer to the *British Journal of Tuberculosis* immediately before his fatal illness:

Nothing has occurred to diminish my faith in the value of tuberculin treatment—a faith which has been manifested by my continuing its use uninterruptedly in my practice and at the Adirondack Cottage Sanitarium ever since it was discovered, and through all the long years I stood nearly alone in my medical environment in its advocacy. If skillfully used, tuberculin stimulates the defensive resources of the organism and is a valuable adjunct to our treatment in many cases. I see no reason why

continued research should not in time give us a better sensitizer than tuberculin.

During the years 1892 to 1895 various tuberculins were introduced that had supposed advantages. Dr. Trudeau expressed the hope that some improvements would be made by which the toxic effects could be eliminated. It was during the period that I began to work with him. Our hopes for the discovery of an efficient vaccine or antitoxin were high at that time. His own time was more than ever occupied with the sanitarium, and his laboratory work was desultory; yet during the winters (the only time he was able to work at all) he continued to direct experiments of the greatest variety. I find on our records over 50 different attempts to immunize animals with dead and living bacilli of varying virulence, and with varying dosage, intervals, etc. These he himself instituted during the years 1892 to 1900, besides numerous other experiments in which he was less directly concerned. At the opening of the Phipps Institute at Philadelphia, in 1903, Dr. Trudeau referred to his successful demonstrations of the immunity reaction obtainable in rabbits as follows:

Most of my own work has been devoted to the study of methods which might tend to produce artificial immunity. . . . It was only when I began to make use of living cultures as a protective inoculation that I met with any encouraging results, and my experience would indicate that the living germ is essential to what success has been attained in the production of artificial immunity against tuberculosis.

By preventive inoculations of living-bird tubercle bacilli in rabbits, I got undoubted evidence of a marked degree of artificial immunity in experiments which I reported to the Association of American Physicians in May, 1893. I was able then to demonstrate to the association, by means of living animals, that in rabbits having previously received the preventive injections of living-bird bacilli, the virulent inoculation at first gave rise to a violent reaction of the tissues, which ended generally in cure, while the tuberculous process similarly induced in the controls was accompanied by little or no local reaction. I have many times since confirmed these results by various experiments. (The History of the Tuberculosis Work at Saranac Lake. *Med. News*, October 24, 1903, p. 8.)

Altogether Dr. Trudeau published but few experimental studies,¹ his periods of ill-health, the sad deaths of his children, and many burdens incident to the sanitarium, made it impossible for him to do more than oversee some of the experiments in which he was most interested. One of his greatest disappointments was the fact that he could not work in the new laboratory generously built for him by Mr. George Cooper in 1894. He often exclaimed that he desired nothing better than a chance to work there and took great pride in showing visitors through.

Only those who knew Dr. Trudeau at home and in his laboratory during his prime could appreciate his enthusiasm for scientific investigation. Those who did not know him in the surroundings that he created whereby he was able to attempt experimental work, quite unique in character for the time, cannot know what pride he had in it. His enthusiasm and pride, nevertheless, never led him to much conceit about his knowl-

¹ Eighteen in all.

edge; this was one virtue that made him so companionable. He was ever modest in assertion, in reality rather timid, even among the young men about him who were naturally deferential. His boasting was too often applied to his associates! A little achievement was always the object of praise from him, and those of us who happened upon some minor point of interest were very likely to hear it enlarged upon by some of our colleagues who had heard of it from Dr. Trudeau.

His manner was irresistibly entertaining to a group of visitors. They often acquired more interest in scientific medicine and were cured of antivivisection heresies by a little talk from Dr. Trudeau about the tubercle bacillus. "Here is a little devil," he would say, "that grows with equal facility in a prince or a pauper," as he exhibited a tube culture to a group of admiring listeners. "Here is what people come to Saranac to be cured of in three months," he would cheerfully remark, as he produced a specimen of extensively cavitated lungs of a rabbit!

While his conversation at such times was dramatic, it was never vain or boastful of his own accomplishments; more often it was of embarrassing predictions of what his assistants were to discover! I can well remember the first weeks in his first laboratory during the winter of 1892 and 1893. He was wont to say: "Baldwin, how does this strike you? If you don't think I'm right I wish you would say so." This was well adapted to increase my conceit in my little stock of knowledge, but it gave a rare impulse to independent thinking. I had never encountered such modesty in any of my teachers and do not think Dr. Trudeau inculcated humility in his associates by this method, though by example this was possible. His belief in research was a passion for its humanitarian service, and he believed in science and humanitarianism joined together. He looked forward to a brighter day when all pain should vanish as a consequence of that union.

In closing I think a favorite expression or aphorism that he frequently used will be of interest to repeat: "The sanitarium represents what we know now, the laboratory what we hope to know in the future."

ARTICLES WRITTEN BY DR. E. L. TRUDEAU, M.D., REPRESENTING HIS EXPERIMENTAL LABORATORY STUDIES.

1. An Experimental Research upon the Infectiousness of Non-Bacillary Phthisis. *Amer. Jour. Med. Sci.*, October, 1885.
2. Environment in its Relation to the Progress of Bacterial Invasion in Tuberculosis. *Amer. Jour. Med. Sci.*, July, 1887; *Trans. Am. Climat. Assn.*, 1887, IV, 131.
3. An Environment Experiment Repeated. *Trans. Am. Climat. Assn.*, 1888, V, 91.
4. Sulphuretted Hydrogen *versus* the Tubercle Bacillus. *Med. News*, 1887, LI, 570.
5. Hydrofluoric Acid as a Destructive Agent to the Tubercle Bacillus. *Med. News*, May 5, 1888, LII, 486.
6. Hot-Air Inhalations in Pulmonary Tuberculosis. *Med. News*, 1889, September 28; *Trans. Assn. Am. Phys.*, 1889, p. 287.
7. Some Cultures of the Tubercle Bacillus, Illustrating Variations in the Mode of Growth and Pathogenic Properties. *Trans. Assn. Am. Phys.*, 1890, V, 183.
8. An Experimental Study of Preventive Inoculation in Tuberculosis. *Med. Record*, 1890, November 22.

9. The Treatment of Experimental Tuberculosis by Koch's Tuberculin, Hunter's Modification, and other Products of the Tubercle Bacillus. *Trans. Assn. Am. Phys.*, 1892, p. 87; *Med. News*, 1892, September 7.
10. Results of the Employment of Tuberculin and its Modifications at the Adirondack Cottage Sanitarium. *Med. News*, 1892, September 10.
11. Eye Tuberculosis and Anti-Tubercular Inoculation in the Rabbit. *Trans. Assn. Am. Phys.*, 1893, p. 108; *N. Y. Med. Jour.*, 1893, July 22.
12. A Report of the Ultimate Results Obtained in Experimental Eye Tuberculosis by Tuberculin Treatment and Anti-Tuberculous Inoculation. *Trans. Assn. Am. Phys.*, 1894, p. 168; *Med. News*, 1894, September 29.
13. A Chemical and Experimental Research on "Anti-Phthisin" (Klebs). (In collaboration with E. R. Baldwin.) *Med. Record*, 1895, December 21.
14. The Tuberculin Test in Incipient and Suspected Pulmonary Tuberculosis. *Med. News*, 1897, May 29, p. 687.
15. The Need of an Improved Technic in the Manufacture of Koch's "TR" Tuberculin. *Med. News*, 1897, August 28, p. 257.
16. Experimental Studies on the Preparation and Effects of Antitoxins for Tuberculosis. (In collaboration with E. R. Baldwin.) *Am. Jour. Med. Sci.*, December, 1898, and January, 1899; résumé in: *Trans. Assn. Am. Phys.*, 1898, p. 111.
17. Artificial Immunity in Experimental Tuberculosis. *N. Y. Med. Jour.*, 1903, July 18; *Trans. Assn. Am. Phys.*, 1903, XVIII, p. 97.
18. Two Experiments in Artificial Immunity against Tuberculosis. *Med. News*, 1905, September 30; *Trans. Nat. Assn. for Study and Prevention of Tuberculosis*, 1905.

DR. JANEWAY: That the president of the New York Academy of Medicine should have left his busy life to come down here to speak to us; that the dean of the Saranac school should have made that long journey to tell us of his knowledge of Dr. Trudeau's career, are eloquent testimony to the esteem and love which Dr. Trudeau, the man, inspired in all who were with him. It has undoubtedly been difficult for the previous speakers to confine themselves strictly to the subject assigned to them.

The last speaker needs no introduction to you, and though he comes but from across the city, he faces no easier task, for his relations with Dr. Trudeau were very close. He will not, however, have to confine himself to any phase of the subject, but will, we all hope, tell us in an intimate way of those sides of Dr. Trudeau's character which, whether we be physicians or not, must appeal to all that is best in us, and must stimulate us to lead in our turn lives which will awake in others those same feelings of respect and of affection which were so universally aroused in everyone who came into any contact with the great physician of Saranac.

DR. TRUDEAU, THE MAN.

BY HENRY M. THOMAS.

It is not easy for me to speak at this time of Dr. Trudeau as a man. He meant more to me than my emotions would stand should I endeavor to tell you. Perhaps the very closeness of our relations obscures my perspective and unfits me for the task.

The oft-quoted saying that "no man is a hero to his valet" did not apply to Dr. Trudeau; indeed, the closer one got to him, the more one admired and loved him. No one who served him ever voluntarily left his service. Dr. Trudeau's power of understanding and sympathy, and his many-sided nature, made it easy for him to get close to a very great variety of people, and if I tell you of my first meeting with him at Saranac Lake, I may be able to give you some idea of his personality, and how simply and unconsciously he allowed it to influence those who came near him.

Just 28 years ago, almost to the day, I went to Saranac Lake. That sounds a simple enough statement now, for many have since traveled the same route. But at that time it may be said that Saranac Lake was practically unknown to the medical profession in Baltimore; actually, I was the second person from here who had ever gone there in search of health. Dr. Trudeau, in his autobiography, gives a graphic picture of the mental state of one who has been ordered to stop work and go away, but I do not believe that it can be understood until it has been experienced.

The circumstances in my own case were such as for the time to abolish any particular desire to live. Dr. Welch, who was my medical adviser in Baltimore, encouraged me in many ways, and assured me that I should be able to continue my work in neuro-pathology in Dr. Trudeau's laboratory, for he was sure that he had a laboratory, as he had done such good laboratory work. Dr. James in New York cheered me on my way, but although I was not very ill, my nervous depression was such that I took three days to make a trip that might have been accomplished in 24 hours. A narrow-gauge railroad from Plattsburg had just been completed to Saranac Lake a few days before, and, if anything could have added to my depression, it was the desolate journey through the snow.

However, it was during this trip that I first became aware of Dr. Trudeau's influence as a man. As I remember it, the only other passenger in the car was a Mr. Krumholtz, who spoke to me and told me something of the place to which we were going. I gathered from him that Saranac Lake and Dr. Trudeau meant practically the same thing, and that the doctor would make it all right for me.

Mr. Krumholtz was my introduction to that ever-increasing company of those whose tuberculosis has been arrested by following the trail blazed by Dr. Trudeau, and I shall never forget his cheerful, helpful talk.

Dr. Trudeau had, in response to a letter, arranged for me to live at the Berkeley, which was then the largest boarding-house for his patients, as well as the village hotel. The talk at dinner on that day among the 15 or 20 guests was of the kind most interesting to lungers, and I thought how depressing such a conversation might be to a non-medical novice. Some of them had during the morning been examined by the doctor, whom they called "The King," and it was not hard to see from the way they spoke and the others listened, and from the questions that were asked, that I had, indeed, come into the domain of a ruler whose word was cheerfully accepted as the law of the land.

That afternoon, while I was unpacking, Dr. Trudeau came to see me. He was a tall, straight man, weighing more than 180 pounds, and his very dress typified the woods and all outdoors. At his heels was his companion, Nigger, a black mongrel, who went everywhere with him except hunting and to church. Dr. Trudeau would not take him hunting, and he never made any attempt to follow him to church.

I am unable to remember what he said to me on that first afternoon, but looking back at it now I think of that interview as the beginning of a friendship that has meant more to me than I can express. I remember this, that in a little while Dr. Trudeau took me out with him, showed me the village, and then left me with a group of young people—patients and their friends—who were tobogganing.

The next morning, which was Sunday, he sent his guide over with a note, saying he did not consider it right that a young doctor, engaged to be married, should eat his Sunday dinner alone, and asking me to take dinner with Mrs. Trudeau and himself.

From that time on I became Nigger's rival, and was with Dr. Trudeau as much as possible; indeed, I both hunted and went to church with him.

Dr. Trudeau, when I first knew him, was 40 years old, and his health was as good as it ever became. Indeed the first impression that he made on me, of a man in vigorous active health, abounding in energy and love of life, was only confirmed by a more intimate knowledge. He was always busy, and the only physical limitation that his disease seemed to have left was his inability to take long walks, skate, run, swim, or row.

His days were full, and he passed quickly from one thing to another, giving to each enthusiastic attention. At this time Saranac Lake was a compact little village in which we were all thrown very closely together. A single stranger in town, or, indeed, a new dog, created remark and had to be explained. There were not many very sick people among us, and as Dr. Trudeau examined his patients only very rarely, some of them only when they came in the fall and when they went out in the spring, and visited them only when there was special need, his winter practice at this time was not very exacting.

The sanitarium was three years old and then contained about 30 patients. The entire management was on his shoulders and, of course, occupied a great deal of his time. He had started almost unconsciously a wonderful institution, and it was amusing to see his assumed consternation at its growth. He would half-jestingly complain bitterly of the load he had to carry, while grasping with avidity every possible chance of increasing it.

He worked some part of every day in his laboratory, which consisted of his narrow office with a boot closet at the end, his barn, and the pit that he had dug in his backyard. As you can well imagine, the hope that Dr. Welch had encouraged in me that I might continue my own work at Saranac Lake vanished the moment I went with Dr. Trudeau into his office, and very soon the desire as well, for after being with him for a

little while I had no other thought than that of doing what I could to help him.

Just at this time many cures for tuberculosis were being advanced, most of them based on the supposed germicidal action of various agents. He tested these and many other things in the hope that he could find something that would kill the organism within the body.

A French observer had stated that men who etched on glass with hydrofluoric acid seldom had tuberculosis, and it was supposed that it was breathing the fumes of this chemical that accounted for the supposed effect. This we tried, and it did, indeed, kill the germ in culture. I saw that he would like to try it on a patient as well as on inoculated animals, and I suggested that I try it on myself. He was somewhat loth to let me do so, but finally consented, and thereafter I sat for two hours a day in a room breathing the fumes of hydrofluoric acid, and with the result that every bit of the glass in the room was etched and that the bacilli disappeared from my expectoration. The rabbits did not fare so well, and although one or two other patients tried it, no further result was obtained.

The deftness and skill which Dr. Trudeau showed in all his actions were very evident in his laboratory technic. Even though the apparatus was simple in the extreme, it was nicely adapted for its purpose and was used by a master workman. One thing in particular I should like to mention, as it never failed to arouse my astonished admiration. The thermostat was heated by a kitchen coal-oil lamp, and Dr. Trudeau regulated the temperature by turning the flame up or down, and opening one or more of the doors of the wooden cases that surrounded the tin box. This was not hard to do during the day while the fires in the house were kept up, but it required skill to arrange for the whole night when the fires went out and everything was apt to freeze. Before going to bed he would look at the barometer on his table, go out-of-doors and look at the thermometer, make an observation of the heavens, and as a result he would turn the flame up or down, and shut or open the various doors. In this way he was able to keep the temperature of the thermostat within the proper limits. How successful he was is shown by the fact that at Saranac Lake living cultures of the tubercle bacillus could even then always be found, and this could be said of nowhere else in the country.

Dr. Trudeau constantly over-estimated other people's attainments and knowledge, and I discovered later that he had looked forward with high expectations to my arrival, as a man who had worked with Dr. Welch in the laboratory of The Johns Hopkins University. His disappointment must have been keen, for I knew little more about bacteriology than I did about hunting.

In later years, when I went with him to the meetings of medical societies, I was often amused, when he had approached some noted physician and told him of the experiments that he was doing and asked for advice about some troublesome point, to note his astonishment when he discovered that it was he himself who was regarded as the authority, and that the other physicians had nothing to offer except respectful attention.

This modest estimate of his own position in the medical world he showed also by requesting all of his patients to be examined frequently by Dr. Loomis or some other consultant to have his opinion confirmed, and he only gave up this habit when the patients flatly refused to regard any other advice than his as necessary, and when he discovered that more and more patients were taking the trip to Saranac Lake to get his confirmation of the advice that had been given by others.

Dr. Trudeau tells in his autobiography how much pleasure he took in getting money for his sanitarium and his other charities; indeed, he put into this quest much the same spirit and craft that he used in hunting game. He does not tell, however, how persistently he shrank from any personal profit that might accrue to himself from the growing reputation of the institutions at Saranac Lake. He, of course, could not avoid charging his private patients, but his fees were always most moderate and usually absurdly small, and at no time commensurate with his reputation. Many of his patients were among the very rich, and at the height of his activity the number who applied to him was very large. He distributed them lavishly among the increasing group of younger doctors who had collected about him, and if I told you the largest sum that he ever made from his practice in one year you would find it difficult to believe me.

Although I am sure that every one of us who was ever associated with Dr. Trudeau in his practice would have been glad to have followed the usual custom in such cases and worked on a percentage basis, that was not his way; he never divided fees, the other man got them in full.

He was unwilling to profit by the work of another man, and he carried this unwillingness to such an extreme that it was at times a check to our offering to assist him. I remember on one occasion I was with him when he prescribed for one of the guests at Paul Smith's. His medicine bag was over at his cottage, and he asked me to get it, and then tried to make me take the fee.

It would be impossible to tell you of his endless generosity to everyone about him. He did, indeed, learn how to beg, but he was a born, incurable giver.

He was extremely sensitive to the groundless fear that some one might think that his advice to patients to remain in the Adirondacks might be controlled in any measure by any possible pecuniary advantage to himself.

The rapid development of Saranac Lake village offered tempting opportunities for investments in real estate, but Dr. Trudeau would never have the least interest in any of the boarding-houses or the many houses that were built for rent to the patients, and, in fact, he got rid of a large tract of land, at no profit to himself, upon which the most extravagant section of the village now stands.

He refused many suggestions by astute business men to become interested in the establishment of private sanatoria. One of these suggestions that particularly aroused his wrath was an offer of \$10,000 a year for his nominal direction of an institution and the use of his name on the circular.

The patients at the sanitarium have always paid much less than it costs to maintain them, and as the sanitarium grew, the annual deficit, as well as the expenses, increased in proportion. It was evident to Dr. Trudeau and to everyone else, that if he would accept well-to-do patients and charge them as they were charged at other sanitariums, the much needed money would be assured. The idea of such a change was never entertained, and Dr. Trudeau kept the institution exclusively for the benefit of those for whom it was designed.

Medicine was not a business to Dr. Trudeau, nor was its study a fascinating response to scientific curiosity. The central, compelling force was a strictly humanitarian desire to do everything that he could to cure tuberculosis, or, if not this, to alleviate the condition of the sufferer as much as possible.

Once having assumed the care of the sick, and having asked and received assistance in his charitable and scientific work, he felt the responsibility very deeply, and gave himself to these objects with absolute unrestraint. It was distressing to him to feel that possibly he might not be measuring up to what he characterized as the "demands of the great public," and he often taxed himself far beyond his strength, in spite of all that his associates and friends could do to shield him. This was particularly so during the summer months when he had charge of the practice among the guests at Paul Smith's Hotel and the campers on the St. Regis Lakes, as well as the responsibility of the sanitarium and his patients at Saranac Lake. In the early years he lived during the summer in his camp on Spitfire, and was rowed to the hotel and about the lakes to see his patients. When he had to go to the sanitarium or village it entailed a drive of 15 miles. As he became more busy, he gave up his camp and lived in a cottage near the hotel.

I wish I could give you some idea of his incessant activities, and the multitudinous demands that were made upon him during these summer months. It was more than any one man could do, and he had to have assistance. I was fortunate enough to be the first to help him, and did so for a number of summers. On the days that he was at Paul Smith's it was possible to relieve the strain somewhat, but on what he came to call the "horrible Tuesdays and Wednesdays," when he went over to Saranac Lake, little could be done. Mrs. Trudeau always went with him on these trips. They left as early as they could and drove to the sanitarium, and then after luncheon to his office at Saranac Lake, where he saw and examined a seemingly endless stream of people who had collected from all over that region of the Adirondacks and come in from the outside to see him. His office hours were repeated again the next morning, and he also had to visit some of his patients who were bed-ridden.

They usually got back to Paul Smith's just before dark on Wednesday, and it was always with apprehension that I met them. Dr. Trudeau was often, as he himself described it, a wreck—absolutely worn out nervously. Time and time again we urged that patients who really wanted his advice would come to Paul Smith's or anywhere else to see him, and that it was wrong for him to put himself to this useless strain. We

were entirely unable to convince him, and he persisted until his health made the trips impossible.

His modesty kept him from believing that many people would take the extra journey to Paul Smith's for his advice, and, more than this, he felt that these weekly trips were a duty to the growing community at Saranac Lake and its neighborhood, and especially to those whose finances would preclude their coming to Paul Smith's.

At the end of each summer Dr. Trudeau was usually wretched, at times with fever and other evidences of the renewed activity of his old process, but more often, at the time I am speaking of, as the result of the strain on his highly strung nervous system. He was subject from his boyhood to extremely sharp attacks of ophthalmic migraine, and was liable to such attacks at any time, but he was almost certain to have them when under any very special strain, as on his Tuesdays and Wednesdays at Saranac, and they were very frequent by the end of the summer.

As is not uncommon with such a make-up, Dr. Trudeau had a very remarkable power of going through with what had to be done, in spite of his feelings, on pure nerve, and paying for it afterwards, and it was only those of us who were very close to him who really knew how he suffered.

His intense interest in hunting and other sports was a great help to him at these times, and we always felt that if we could get him down to Little Rapids, and into the woods with his old guide and friend, Fitz Hallock, that his astonishing recuperative power would again restore the balance.

Soon after I first went to Saranac Lake I started hunting with Dr. Trudeau, and two or three times a week his guide, Parker, would appear at the Berkeley, while I was at breakfast, with a note asking me to come over to the house a little earlier, as there was something he had for me to do.

I soon learned that this "something" meant that there was a hunt planned, and I expected to find, when I got across the street, his sleigh at the door, with Bunnie, his favorite hunting dog, hitched to the back, and the guns hidden under the lap robes. There was always a certain amount of secrecy connected with these expeditions, and we got out of the village with as little fuss as possible, the idea being not to reveal the location of the rabbit swamps to the other sportsmen. It was a rare hunt that was unsuccessful, for we had along the best shot and the best rabbit dog in the woods, but it was a very rare hunt, indeed, in which I killed the rabbit.

Dr. Trudeau's patience with my clumsiness and awkwardness in the woods was boundless, but at times he could not refrain later from describing to Mrs. Trudeau in his inimitable way how I, by moving my feet, or taking the wrong position, or by missing an easy shot first with one barrel and then with the other, had managed to cheat Bunnie of the satisfaction of finding his rabbit dead at the end of a long and intricate hunt.

Dr. Trudeau was a keen hunter and an almost perfect shot, but even at this time his scientific work, his sanitarium, and his practice, were occupying so much of his time that he had become the physician who hunted for recreation instead of the

sportsman who occasionally prescribed for a patient because he had to. He had entirely given up fox hunting as that required too much time, but three or four times a week he and I would go into the woods and hunt rabbits for an hour or two. A good rabbit dog was something that he insisted upon having. He tried out every kind of hound that seemed promising, and Fitz Hallock always had two or three dogs in training, many of which were the result of experimental breeding.

At this time of his life he was rarely able to get the time to hunt deer, and it was not until later, when he became part owner of Little Rapids, a hunting preserve, that he did so with any regularity.

Next to hunting and fishing his chief sporting interest was in relation to sailing. He and Mr. Anson Phelps Stokes inaugurated the sail-boat races on the upper St. Regis Lakes, and were keen rivals for a number of years, but here again his professional duties had interfered by the time I became very familiar with the summer life of the Adirondacks, and he had turned this phase of his activities over to the efficient care of his son Ned. He always loved a good horse and always owned one.

His enthusiasm for almost all kinds of sports and his remarkable skill in most of them made it easy for him to get into close sympathy with many of his patients who cared but little for his other activities, and they took unquestioned his advice about their health and the management of their lives when they learned how good his knowledge was about the things that they themselves knew.

Trudeau the man, and that means the physician, the scientist, the philanthropist, and the friend, cannot be understood without some knowledge of his intimate home life. Fortunately, he has himself on many occasions, and most beautifully in his autobiography, acknowledged his dependence on the quiet, strong, ennobling, unselfish influence of his wife. Without Mrs. Trudeau I do not believe that Dr. Trudeau, as we knew him, would have been possible—she so perfectly supplemented his high-strung, emotional nature. Always, but especially so in times of discouragement, sickness and sorrow, she gave him with perfect understanding just the help he needed.

I cannot brave the attempt to describe the home life of the Trudeau family, nor to estimate the privilege it was to many of us to share it in some degree. Dr. Trudeau's life at home differed in no essential particular from his life that was open to the whole world; indeed, all of his activities were centered there, and it was there only that one was able to get a clear idea of all the various channels through which his influence went out to the public.

Mrs. Trudeau sympathized in all of her husband's aims, but she was, I think, the directing force in his work of building churches and maintaining them. Dr. Trudeau was a deeply religious man, but cared little for creeds or doctrinal theology, although he was a consistent Episcopalian. His sustaining optimism was based on his faith, and it was this that he believed enabled him to accomplish some of the things that his vision set before him. He has beautifully expressed this as a farewell message to the medical profession in his address on

"Optimism in Medicine." He radiated this message of faith and optimism constantly to his patients and those about him, although he preached it but rarely.

Dr. Trudeau had a remarkable facility for letter writing, and the letters that he wrote were innumerable. When he was well and in full activity, he would occupy every spare moment with his correspondence. It made little difference to him how many people were in the room or what they were doing. One of the clearest pictures I have of him at home is sitting at his desk surrounded by a roomful of talking and laughing people, who would interrupt him constantly while he wrote letter after letter, throwing each finished one on the floor until the rug at his feet began to resemble the snow-covered world outside. For many years he had no secretary and wrote all of his letters himself; indeed, to the end of his life he acknowledged every contribution to the sanitarium with a personal note. He wrote a long letter to his mother every Sunday of the many years that they were separated, and even more frequently to his sons, Ned and Francis, while they were away from home being educated, and more rarely to other members of his family. He also corresponded regularly with a host of friends and patients.

I think there must have been very few sick people indeed who had been under Dr. Trudeau's care who ever stopped regarding him as their chief adviser. Certain it is that he was getting letters constantly from all over the world from former patients asking his advice and counsel about any contemplated step that seemed to them important. In some instances, where he had advised patients to leave the Adirondacks because the disease was so far advanced as to exclude all hope of its arrest, or for some other reason, he kept in intimate touch with these patients and managed to send them something of his sustaining personality.

Since Dr. Trudeau's death I have had sent me a series of letters he wrote to a patient, and I would that I could read them all to you.

This patient, a young woman, had gone to Saranac partly through my advice, but, unfortunately, the process in her case was steadily progressive, and Dr. Trudeau had from the first little hope that it could be arrested. The hopelessness of the condition stimulated, as it always did, his desire to help and, after she had left the Adirondacks with no thought of returning, he wrote to her frequently, intimate gossip letters, but each containing some suggestion, either as to the details of her management, or some thought meant to help her bear the inevitable decline.

Once he wrote two long, patient letters, explaining to her the uselessness of a troublesome and somewhat quackish treatment that she had been urged to take by members of her family.

At another time, towards the end of her illness, he uses his authority to protect her from the well-meant but bothersome attentions of a nursing friend. I shall read you this letter.

Dec. 17, 1895.

DEAR MARY,

I was very much amused at your letter and the cause of your trial. Indeed, it is just what I expected, but I refrained from expressing any opinion of the young lady because I understood she was coming as a friend as well as a nurse. Her letter was the most

impossible, impracticable kind of twaddle I ever read, and I would have sent it to you to laugh at had it not contained some inquiries about your ailments and yourself which would have annoyed you and which, of course, I did not answer. If she shewed my answer you will see I didn't say very much! As I did not know her I hardly felt she had a right to write me about you and your affairs as she did. You can say most emphatically from me that I think a temperature chart is a very bad thing for you to keep, and I don't even like you to use a thermometer and never except when you feel sick enough to want to go to bed and need to know for that reason. The salt sponge is all right, of course, if you choose to take it. I wish I were there to lay down the law to your friend, and I can see she must be rubbing you up the wrong way all the time and making your illness all the harder to bear. You see I am just conceited enough to think I understand you a little. Don't let anybody bother you; it is against the doctor's orders.

And with love believe me,

Most sincerely,

E. L. TRUDEAU.

Dr. Trudeau never came very close to a patient without getting into touch with the patient's inner spiritual life, and it was an unusual person who was not better for having known him.

Another letter, evidently an answer to one which uncovered some of the innermost feelings of this patient's sensitive and reticent nature, is very characteristic:

APRIL 13, 1895.

Your sweet letter to me was a great pleasure, and you may be sure I appreciate the confidence you have given me so fully. I will never say any more about your cold nature again, but I never meant any of it and only wanted the visible proof of what I knew so well was there all the time if I could only be so fortunate as to call it out.

I am very glad to hear you had so comfortable a journey and had a look at the pomps and vanities, as I think you need all of that side of life that comes in your way, for I have, I assure you, appreciated and felt all you have had to go through here and wished I could help you, but we must each walk the thorny path which leads through suffering, if we would learn to look over and beyond, and to know the peace which all the trials of life only intensify for us.

This patient was only one of very many to whom he wrote such letters, and if it were possible to collect them, they would make a lasting record of his treatment of tuberculosis and his management of patients who were suffering from that disease.

Dr. Trudeau never complained of the tax upon his time and strength which his personal correspondence demanded, but when his mail was full of letters from hopeless invalids demanding immediate admittance to the sanitarium, and from strangers asking advice, scientific or otherwise, and a host of other such things, he was apt to rebel. But nothing aroused his indignation so quickly as when some luckless correspondent intimated that he would gladly compensate him with money for some special privilege or service.

During the last years of his life Dr. Trudeau had the help of a stenographer, but even with this alleviation his correspondence was so great that some of his closest friends refrained from writing to him as often as they wished in order to spare him, and begged him when he wrote to send them dictated letters. Dr. Trudeau never learned to express himself with

the same freedom and ease when dictating as when he wrote by hand. Nearly all of his scientific articles were so written and the whole of his autobiography, and during times of stress and illness he found comfort and relief to his emotional nature in writing unreservedly to his most intimate friends.

The writing of his autobiography was a great surprise to himself. He had refused many offers from people who wanted to write his life and had resisted the urging of friends that he should himself write down his own experiences, and only succumbed at last to the kindly insistence of Dr. James, and consented to make the attempt. He began with very little hope of having either the ability or strength to complete it, but, when he had commenced, his wonderful enthusiasm came to his aid, and as the work progressed he became conscious of powers that he had no knowledge of possessing. When asked how he could write so vividly of scenes long past, he said that he recalled them to mind largely as visual images and wrote describing what he saw as rapidly as possible. He wrote on small sheets, often erasing and correcting them until they were almost illegible, and from these his secretary made the typewritten copy which rarely required the least correction.

I am conscious how very imperfectly I have been able to convey to you any adequate idea of Dr. Trudeau's personality. His was a nature that appealed instantly to everyone who met him, and it was easy for him to influence even casual acquaintances. He used this power with great skill in controlling his patients, and getting assistance for his charitable work. Men and women gave him without stint their unremunerated labor, and others delighted to help him with their money. I have time after time watched for and seen this instant response to his personality as he met and talked with strangers. This power which he retained to the last is shown very beautifully in the account which Mr. Clayton Hamilton, in his recent book, "On the Trail of Stevenson," gives of his single interview with Dr. Trudeau. The trail had led Mr. Hamilton to Saranac Lake in the Christmas season of 1911, where he saw Dr. Trudeau, who was then ill and sitting out on his little porch. They talked about Stevenson and of Dr. Trudeau's own work. Among other reminiscences, Dr. Trudeau recounted, as he delighted in doing, Stevenson's remark on the one occasion in which he had been decoyed into the laboratory. Stevenson, after looking for a little while at the cultures and specimens, said about as follows: "Trudeau, we both are bearing lanterns, but I must say yours smells to me most confoundingly of coal-oil."

In relation to this story Mr. Hamilton writes:

The doctor told me this with humor; but it did not seem to me so funny when I thought about it afterward. At present I remember an eager, active-minded man sitting anchored in a lounging chair and muffled among furs; talking with that tense voice of the achieving dreamer; at home in life, though exiled from its laughing and delightful commonplaces; cheerful and alert, though slowly dying; young, clear-eyed, and still enthusiastic, although already ancient in endurance; lying invalidated while his City of the Sick grows yearly to greater prominence among the pines; fighting with an easy smile the death that has so long besieged him, to the end that others after him, afflicted similarly, may not die.

And the best of our tricky and trivial achievements in setting words together dwindle in my mind to indistinction beside the labors and the spirit of this man.

DR. JANEWAY: One impression, which I hope will be a lasting one, I think we will all carry away with us to-night. It is that, in our medical heroes it is impossible to separate the professional life and the personal character. That is not true in all professions, and certainly not true of all heroes. It lays upon those of us who are their successors in the medical profession to see to it that we are true both to their scientific and humanitarian ideals as physicians, and to the legacy of rich character and sympathy with suffering which they have left to us as men and women.

I am going to ask Dr. Thayer if he will express our thanks to the gentlemen who have so kindly come here to read these splendid tributes.

DR. THAYER: May I first add a word about one phase of Dr. Trudeau's activities which has always impressed me deeply?

Dr. James has spoken of his diagnostic and prognostic abilities. These he used for years with wisdom and skill in determining just who, among the many patients who presented themselves as applicants for admission to the sanitarium, were most likely to be benefited by the advantages which it offered. As he has said himself, this was not an easy task; it was one in the exercise of which he was often criticised; but it was precisely those patients in whom the process was at its earliest stages, to whom the sanitarium was especially likely to give that help which might turn the scale. From this standpoint Dr. Trudeau exercised remarkable ability and discrimination. But often he went farther and exercised an insight and a charity so exquisite that those of us who have experienced it can never forget. He knew not only how to choose those whose lives were most likely to be saved; he knew how to choose those whose lives were most worth saving.

Some of us have had the experience of sending to him patients whose symptoms were not so favorable as, under ordi-

nary circumstances, to justify admission to the sanitarium, yet patients whose character and circumstances were such as to appeal to us with peculiar force. We have sent him such patients without, perhaps, even a suggestion that they be admitted to the sanitarium. How quickly under these circumstances did his clear eye and his generous heart detect the great opportunity!

He who has seen the group of men and women gathered in that sanitarium can hardly have failed to realize that this was no ordinary collection of individuals, but a body of the elect. How many to whom all doors of hope seemed closed are now living happy and useful lives, thanks to the skill and insight and charity of this great and good man.

Those who knew Dr. Trudeau in his latter years were more and more impressed with the beauty of his face. It was not the beauty of line or of color such as one sees in the young, but a beauty brought out by crease and furrow and hollow, that beauty which character brings to age. Bradford tells of a well-known statesman that when spoken to of a certain man, he exclaimed: "I do not like him. I do not like his face." "That is not his fault," said his friend, "he's not responsible for his face." "Yes," he replied, "every man over fifty is responsible for his face." I have thought of that remark when looking into Dr. Trudeau's face. It was a wonderful face with a singular beauty and depth of expression. In the later days when sorrow and illness had settled upon him, it seemed sometimes as if the body had almost gone, as if nothing remained but the spirit which glowed in the light that shone from his eyes. The body has gone now, but the spirit remains, burning in the hearts of thousands of men and women whom he has taught to live, animating that fine body of students who are carrying on his great work at Saranac and handed on by them to us to-night.

We can hardly express deeply enough our gratitude to Dr. James and to Dr. Baldwin and to Dr. Thomas for what they have said to us. This is an evening that we shall all remember.

POST-PARTUM CARE OF THE PERINEUM.

By E. D. PLASS, A. B., M. D.,

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The present treatment of the perineum both after uncomplicated labor and after primary perineorrhaphy appears to have descended from the antiseptic period, when any addition to the chemical armamentarium was hailed as a panacea. It would seem that obstetricians have been so absorbed in determining the proper time for, and the technique of, repair, that the old antiseptic after-care has been handed down unchanged to the present generation. Only occasionally a skeptic like Krönig has dared to doubt the value of these time-honored customs, but in the course of time all of us will be led to consider critically the value of antiseptics, and determine to what extent they are useful.

When it is realized that, with the exception of iodine, the usual antiseptics, in concentrations in which they can safely be used on the skin, destroy the usual pathogenic organisms only after a long period of activity, does it appear reasonable to expect that the ordinary irrigations and douches will have more than a mere mechanical action? The false sense of security engendered by the term "antiseptic" is dangerous, and when untoward results follow, many individuals seemingly prefer to lay the blame upon the solutions rather than upon their own slipshod methods. To the average nurse the term "antiseptic" spells safety, and she trusts implicitly in the germicidal action of a 1:1,000 or even 1:2,000 carbolic solution.

By eliminating the use of such solutions we do away with this false sense of security, and in my experience the results will be as good or better than those formerly obtained.

There is practically no recent literature upon the routine post-partum care of the perineum, or the after-care of primary perineal repairs. In order to ascertain the general sentiment of the obstetricians of this country in this regard, various text-books of obstetrics were examined with the following results:

E. P. Davis (Manual of Obstetrics, 1914) advises "a copious irrigation by a small pitcher with an antiseptic solution," during the puerperium, and "pouring 1% lysol or sterile salt solution from a pitcher over the parts after each micturition or defecation and whenever the vulvar dressing has become soiled and has been removed," in the after-care of cases with suture.

Hirst (Text-Book of Obstetrics, 7th edition, 1914) says: "Care must be exercised to remove blood and blood clots from the vulva before putrefaction sets in. This is best done by placing the woman on a bedpan, letting a stream of boiled water run over the parts, and, if necessary, using cotton to wipe them off." No reference to any special care after perineorrhaphy was found; but since Hirst advises making all repairs at the end of one week, one can scarcely speak of primary repair.

Henry F. Lewis, in the Practice of Obstetrics, edited by R. Peterson, 1907, advises "irrigation with sterile water or sterile antiseptic solution, finishing by drying with some sterile gauze." He mentions no special care following repair.

De Lee (The Principles and Practice of Obstetrics, 1913), under "Aseptic care during the puerperium," says: "The patient is placed on a sterile bedpan, the nurse sterilizes her hands or wears sterile gloves, and gently pours from a narrow-tipped pitcher a solution of 1:2000 bichloride over the vulva. The excess is dried off without rubbing, by touching with dry sterile cotton . . . Simple sterile water may be used." After repairs no special care is recommended.

Without exception the text-books examined recommended cleansing at frequent intervals with antiseptic solutions, with sterile water or with saline solution, and frequently the procedure was made very elaborate and time-consuming. There seems to be a widespread belief that some extra care is needed, but the variations in treatment have to do only with the choice of the solutions and in the method of their use.

In order to demonstrate whether such routine antiseptic treatment of the perineum after delivery has any distinctly beneficial effect upon the course of the puerperium or upon the healing of primary perineal repairs, the following clinical experiment was conducted. For a period of nine months—from November, 1914, to August, 1915—all patients were divided into two groups after delivery, A and B (every alternate patient being placed in group A), and treated as follows: Those in group A were given the routine perineal care and those in group B were given no special attention. The routine care consisted in bathing the vulva and perineum with cotton pledgets soaked in 1:2000 bichloride of mercury solution every four hours, as well as after each defecation and urination during the nine days the patient remained in bed. The patients in

group B were merely kept macroscopically clean with warm tap-water and soap and a wash cloth. No attention was paid to voiding or bowel movements, unless, as sometimes happened after the initial dose of cathartic, the need of cleansing the parts was apparent. The bloody lochia were removed whenever necessary. Unless the patient was very ill, she was expected to keep herself clean. It was found that the average number of cleansings necessary was as follows: Four a day for the first three days, between the third and sixth days not more than two a day, and after this only one, at the time the morning bath was taken.

Every effort was made to eliminate any factors which might invalidate our conclusions. Since the two series were run simultaneously, the factors of nursing care and surgical ability in repairing the lacerations on the part of the house staff were removed as nearly as possible. The head nurse arranged the lists impartially and none of the staff knew how any particular patient was being cared for. No exceptions were made to the alternate grouping of the patients. At the end of the experiment, when each group contained 200 cases, the records were carefully tabulated and the following facts discovered:

TABLE A.

	Group A. Routine Care.		Group B. Soap and Water Care.	
Primiparae.....	120	60%	102	51%
Multiparae.....	80	40%	98	49%
Full term deliveries.....	181	90.5%	174	87.0%
Premature labors (7-9 months)....	16	8.0%	21	10.5%
Abortions (under 7 months).....	3	1.5%	5	2.5%
Spontaneous deliveries.....	185	92.5%	185	92.5%
Operative deliveries.....	15	7.5%	15	7.5%
Vaginal examinations.....	93	46.5%	92	46.0%
Temperature never over 100.4° F.....	121	60.5%	128	64.0%
Temperature over 100.4° F.....	79	39.5%	72	36.0%
Elevation due to uterine infection..	30	15.0%	29	14.5%

Reference to Table A shows that the two series are quite comparable as regards operative deliveries and the frequency of vaginal examinations, the two factors which might possibly have had a bearing on the results. The total morbidity (temperature over 100.4° F., taken every four hours) is approximately the same (group A, 39.5%; group B, 36.0%); nor is there any striking difference in the incidence of elevation of temperature attributable to uterine infection, as determined by uterine cultures or by the clinical course of the puerperium (group A, 15.0%; group B, 14.5%). The advantage, if any, is in favor of the series not especially treated (group B).

The low percentage of vaginal examinations is attributable to the fact that the staff attempts to follow the course of labor by means of abdominal palpation and rectal examination, so that ordinarily vaginal examinations are made only for the purpose of instructing students. These, however, probably account, in part at least, for the rather high morbidity, particularly that referred to uterine infection. Fortunately, none of the infections were severe, and there was no mortality.

The number and character of the repairs of lacerations, as well as the conditions which obtained at discharge (12 to 14 days after labor) are shown in Table B. No particular scheme of repair was insisted upon, but all perineorrhaphies were made with catgut and silk-worm gut, either singly or in combination. Very small nicks were frequently not repaired.

TABLE B.

	Routine Care.		Soap and Water Care.	
	Well healed.	Poorly healed.	Well healed.	Poorly healed.
1st degree...	39 92.8%	3 7.2%	29* 96.6%	1 3.4%
2d degree...	21 75.0%	7 25.0%	19† 95.0%	1 5.0%
3d degree...	0	0	1 100.0%	0
Totals....	60 85.7%	10 14.3%	49 96.1%	2 3.9%

* One patient died eight hours after delivery (eclampsia).

† In one case, no repair (eclampsia).

It will be noticed at once that there is a considerable difference in the results obtained. The routine care was followed by many poor results, whereas excellent results were obtained where no antiseptic precautions were taken. Of special interest is the one case of complete laceration—a forceps delivery of a child weighing 5000 g. in the case of an 18-year-old primipara. She chronologically went into the “no care” list, and the supreme test was made. The healing was *per primam*, and not only was the sphincter tone excellent, but the perineal body was also in good condition. When one sees a poor result in only 12 out of 400 cases there is a tendency to be satisfied; but a comparison of the results obtained in the two groups—14.3% and 4%, respectively—clearly indicates that too many failures occurred in group A.

This method of treatment was so successful that on August 1, 1915, the old routine was entirely abandoned. Since that time 57 primary perineorrhaphies have been done as follows: 1st degree, 32; 2d degree, 17; and episiotomies, 8, with only three bad results (5.25%), and these were confined to the first degree tears. The episiotomies were all lateral, single or double, and the wound healed *per primam*.

To date we have treated 108 repairs in this manner and have had five failures, a percentage of 4.6.

In addition to the better results obtained after the elimination of the more or less complicated antiseptic treatment, there is an economy in the time of the nurses. All who have to do with nursing in large institutions will welcome any change which will free the nurses from the burden of unnecessary routine and give them time to really nurse the patients, provided the result is satisfactory.

Conclusions.—The use of antiseptic solutions in the care of the perineum during the puerperium or in the after-care of primary perineorrhaphies is of no value.

Macroscopic cleanliness alone gives better results and effects a considerable saving of time.

NOTE.—Since November, 1914, the antiseptic after-care of secondary perineorrhaphies done on the gynecological service has been discontinued and no attention is now paid to the wound in these cases. Dr. V. N. Leonard, resident gynecologist, has assured me that the results are excellent; and that, although no statistics have been compiled, the percentage of poor results is even less than previously. The absence of bleeding makes it unnecessary to resort to any special cleaning of the perineum so that the only attention consists of the usual morning bath. Vulvar pads are discontinued after two days.

THE CASES OF GAUCHER'S DISEASE REPORTED BY DRs. KNOX, WAHL AND SCHMEISSER.

By F. S. MANDLEBAUM, M. D., and HAL DOWNEY, PH. D.

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In the paper by Brill and Mandelbaum on Gaucher's Disease (1913) an attempt was made to show that this disease is a distinctive clinical and pathological entity, easily differentiated from a large group of diseases whose chief characteristic is an enlargement of the spleen. These authors called attention at the time to a considerable number of cases quoted in the literature as instances of Gaucher's disease without sufficient clinical or pathological data to warrant the diagnosis, and hoped that the subject would not be confused in the future by the addition of other unproven cases.

In the paper by Drs. Knox, Wahl and Schmeisser, which has just appeared in the BULLETIN of The Johns Hopkins Hospital,¹ two cases of Gaucher's disease in infants are reported, which, in our opinion, should not have been so classified.

We are able to show that the diagnosis is unwarranted, not only by our analysis of the histo-pathology and microchemical tests as reported, but also because we had an opportunity of studying a portion of the material which was kindly sent to us by Dr. Wahl in June, 1914. At that time we came to the conclusion that the case (Case I) was not one of Gaucher's disease and called the attention of Dr. Wahl to this fact.

In an analysis of recently reported cases of Gaucher's disease, in a paper now in press in the *Folia Haematologica*, we decided not to comment upon the cases which were reported by Knox and Wahl in a preliminary communication while our article was in preparation, but preferred to wait until their full report appeared.

From the very limited number of cases of Gaucher's disease reported in infancy one is not warranted in describing a constant or definite clinical picture, for the disease at this age has

¹ Vol. XXVII, Jan., 1916.

usually been complicated by intercurrent affections of one sort or another. Still, one must bear in mind the fact that, whenever a reliable history is obtained, it will be found that most, if not all, cases observed in later periods of life, have originated in infancy or childhood. Inasmuch as one of the chief characteristics of Gaucher's disease is its essential chronicity, it must not necessarily be considered a fatal disease when occurring in infancy, even though the individual may succumb to some complicating affection. For these reasons it is unnecessary to enter into a discussion here of the clinical features at this period of life, in which the diagnosis may be difficult if not impossible.

We admit that the histo-pathology in any case of Gaucher's disease at its very inception would probably show but few cellular changes. Inasmuch as no autopsy findings at this earliest stage have ever been reported, we may assume that the diagnosis might be impossible. In the case just described by Drs. Knox, Wahl and Schmeisser, however, the cellular process is so far advanced that the normal appearance of many of the affected organs is almost entirely effaced. One might reasonably expect, therefore, to find at least some resemblance to the lesions of Gaucher's disease in a process so well established and so widespread in its manifestations. This, however, is not the case, as will be shown later. Moreover, in the case reported by Niemann, in which the disease began at the age of two months, the lesions 15 months later were limited to the hematopoietic organs and the histo-pathology is that of Gaucher's disease. Furthermore, the patient of Erdmann and Moorhead, upon whom a splenectomy was performed at the age of three years and four months, presented an enlarged spleen at the age of 14 months, and here also the histological examination shows the characteristic changes of Gaucher's disease.

From a study of the complete autopsy material in three of our own cases ranging from the age of four and one-half years to 42 years, together with the findings of six other observers whose cases also came to autopsy, we find it difficult to believe that a definite pathological process, limited invariably to the hematopoietic organs, could have originated in infancy or childhood as a widespread lesion involving the heart, lungs, pancreas, kidneys, adrenals, intestines, thymus, brain, and other organs. It is equally difficult to realize that the lesions described by Drs. Knox, Wahl and Schmeisser, which have no resemblance whatever to those of Gaucher's disease, could become localized in later life to the hematopoietic organs and conform to the well recognized picture of this disease.

In considering the histo-pathology of these cases we shall confine ourselves entirely to the results of our study of material from Case I. This consists of spleen, liver, lymph node and adrenal body. In the first place, it is quite evident that all sorts of tissues are involved in the process, particularly the parenchyma of the various viscera, as is freely admitted by the authors. This constitutes one of the most marked differences between these cases and the authentic cases of Gaucher's disease. In the liver there is no question but what the majority of the large, vacuolated cells are derived from the

hepatic cells. A few vacuolated cells are seen in the periportal connective tissue, but there is practically no increase in the amount of interstitial tissue, and consequently the number of large cells from this source is very insignificant. The liver from a case of Gaucher's disease presents a totally different appearance. It shows a tremendous increase in the amount of interstitial connective tissue, both periblobular and intralobular. This interstitial tissue is crowded with the characteristic Gaucher cells, and it is quite evident that these have not been derived from the hepatic cells. Although the hepatic trabeculae are more or less broken up by the invasion of Gaucher cells, the liver cells remain quite normal in appearance. In the case under discussion, the epithelial cells of the larger bile ducts are very much vacuolated, and conspicuous vacuoles are also seen in some of the endothelial cells of the larger vessels and also in a few of the stellate cells lining the sinusoids. In Gaucher's disease, even in the most advanced stages of the process, such changes in the bile ducts, sinusoids and endothelial cells of the vessels were never seen. The process is limited strictly to the interstitial tissue of the liver.

In the lymph nodes there are many differences between Gaucher's disease and the case of Drs. Knox, Wahl and Schmeisser. In the latter, the node is packed rather uniformly with the large, clear, vacuolated cells, although in parts of the node there is some grouping of these cells into rounded masses which are surrounded by sinuses or thin layers of connective tissue. These rounded masses seem to be medullary cords which have become rounded owing to the accumulation of foam-cells. In other parts of the node the large cells are quite uniformly distributed. In Gaucher's disease this grouping of the characteristic cells in rounded masses is much more conspicuous than in this case.

The long strands of modified tissue described by Bovaird, Risel, and by the writers in their forth-coming paper, are not present in this case. These long strands, which show clearly that the characteristic cells are derived from the reticulum, are very characteristic for Gaucher's disease, and their total absence in the present case is a strong argument against classifying the case with Gaucher's disease. Another feature which does not correspond to conditions in Gaucher's disease is the reduction in the amount of the reticular tissue of the node. To a certain extent this is replaced by many strands of young white fibrous tissue which grow into the node from the capsule, carrying many thin-walled vessels and capillaries with them. The reduction in the amount of the reticulum makes these capillaries appear very prominent. Such a condition has not been reported in Gaucher's disease.

In the node available for our study the process was so far advanced that it was impossible to determine the source of the large cells. However, the presence of a few abnormally vacuolated lymphocytes seems to indicate that some of the large cells are transformed lymphocytes.

In the spleen the pathological process is just as far advanced as it is in the early case of Gaucher's disease which has already been reported by one of us. Although the organ is packed with large, clear cells, there are many points of detail wherein it

differs from the spleens of the Gaucher cases reported. The enormously enlarged sinuses surrounded by rather thick connective tissue walls, which are so characteristic of the Gaucher spleens, are not seen here. The photomicrographs, figures 1-4 published in the paper under consideration, when compared with those published by Mandlebaum (*Jour. Exper. Med.*, Vol. 16, plates 78 and 79), show the difference clearly enough. In the Gaucher spleen there are a few normal sinuses, but most of them are greatly modified and they are usually without an endothelial lining, although they may be lined with one or two layers of Gaucher cells. In the case under discussion, although the process is far advanced, most of the sinuses are fairly normal in size and appearance, except for the fact that their endothelial cells are usually somewhat swollen.

In the Gaucher spleens the characteristic cells located between the sinuses are arranged in the form of rounded solid masses, or as alveoli, which are surrounded by thick bands of fibrous tissue. Some such arrangement occurs in the spleen of the case under consideration, but the masses are not nearly so clearly outlined as is the case in Gaucher's disease. In other words, the organ is much more uniform in appearance than is the case in Gaucher's disease. The large cells are similar to those of the lymph node and liver, but they are very different from the characteristic cells of Gaucher's disease.

In the adrenal body it is clear that all parts of the organ are affected by the process, the cells of the zona reticulosa most. Cells of the zona glomerulosa are vacuolated, and also those of the zona radiata. In the lower portion of the latter zone the nuclei are small and irregular, but the cells are not materially enlarged in these two regions. The cells of the zona reticulosa show the greatest amount of change. These cells are very large and very much vacuolated, and they have the same characters as the cells in the other organs. Rounded groups of these cells are surrounded by bands of fibrous tissue, and in this respect the adrenal bodies suggest Gaucher's disease more than do any of the other organs examined.

The cells of the medulla are also affected, but they have not enlarged to the same extent as those in the zona reticulosa. They are still quite dark and can be recognized as medullary cells. Their nuclei are fairly normal.

It is perfectly evident from the above, as was also pointed out by Drs. Knox, Wahl and Schmeisser, that the large vacuolated cells are derived from the parenchyma of the organ, chiefly the zona reticulosa. But that part of the organ which one would expect to find modified, if this were merely an extension to the adrenal body of the characteristic pathological process of Gaucher's disease, namely the supporting framework, shows little or no change, excepting that it is slightly increased in amount. In Gaucher's disease, no matter how far advanced the process, the reticular tissue of the hematopoietic organs and the supporting tissue of the liver are the only tissues involved.

It is claimed that the large vacuolated cells, which characterize the organs of this case, are identical in structure with those which have been described for Gaucher's disease. Even a superficial examination shows that this is not true. The

nuclei are quite similar in structure and shape, although multinucleated cells are far more frequent in Gaucher's disease. In other respects, however, the cells are quite dissimilar. In Gaucher's disease the large cells present a very peculiar appearance which is not exactly duplicated in any other pathological process. The stainable portion of the cytoplasm occurs in the form of a network composed of rather fine fibrils, the main strands of which take a more or less parallel, wavy course, in the direction of the longitudinal axis of the cell. Even in the more rounded cells the fibrils show a tendency towards a more or less parallel, wavy course across the cell, in case its nucleus is eccentric; or they encircle the nucleus, if the latter is near the center of the cell. In other cells the course of the fibrils is more complicated, but the main strands of the network show the same tendency towards parallelism. This gives the cells a peculiar streaked appearance which is very characteristic for Gaucher's disease, and which distinguishes its characteristic cells from those of the case under consideration and from those figured by Schultze and Anitschkow. Frequently the bands of fibers appear crowded apart in such a way that they form a rather distinct wall around elongated or irregular colorless spaces. Rounded, vacuole-like spaces are very infrequent, which is another point of distinction between the cells of Gaucher's disease and those of the lipoidemia cases and the case of Drs. Knox, Wahl and Schmeisser. These differences are brought out very clearly by a comparison of the figures published by Anitschkow (*Ziegler's Beiträge*, Bd. 57, Plate 8) with Risel's Figure 2 on Plate 6 (*Ziegler's Beiträge*, Bd. 46).

The large cells of the case of Drs. Knox, Wahl and Schmeisser are seen to be identical with those figured and described by Anitschkow, Schultze and Lutz, but very different from the cells seen in true Gaucher's disease. The cells are more rounded than are most of the Gaucher cells, and their cytoplasm is filled with rounded vacuoles—a condition which is very rare in Gaucher cells—and the longitudinal striations are absent. Since the presence of lipoids was demonstrated in these cells and in those from the lipoidemia cases of Schultze and Lutz and in the experimental animals of Anitschkow, it seems evident that this type of cell is characteristic for lipoidemia, but not for Gaucher's disease. These cells are never fused into greatly elongated strands and syncytial masses as is the case in Gaucher's disease (Risel, Bovard). This constitutes one of the most important differences between the two types of cases and one which, with the streaked appearance of the cytoplasm of the Gaucher cells and the preservation of the non-stainable portion of the cytoplasm after treatment of the tissues by the usual histological methods, permits unflinching diagnosis of Gaucher's disease, especially when it is remembered that the supporting framework of the hematopoietic organs and of the liver are the only tissues involved in the process.

Let us consider for a moment the microchemical examinations which are reported in the first case only. It is stated that the substance in the large cells disappears on treatment with absolute alcohol or ether and is slightly refractile. The staining reactions with Sudan III, Nile blue, neutral red,

Gaucher's method, and the Weigert-Pal myelin sheath stain, while not altogether convincing as to the specific type of lipid matter present, give certain reactions. Anisotropic bodies are seen after the myelin sheath stain. It is stated that these reactions suggest the presence of some fat-like substance that may be in the process of transformation into neutral fat and may represent an intermediate stage between the latter and a closely bound molecule of protein and fat. In other words, some substance of a lipid nature, resembling myelin and closely related to the fats, is found by microchemical tests.

The material which Dr. Wahl kindly put at our disposal had previously been placed in alcohol, therefore we were unable to make microchemical tests for lipoids. The opportunity of studying the lipid question, however, was afforded us through the kindness of Dr. Bernstein, from whom we obtained material from two cases of Gaucher's disease in children. Our examinations were made on frozen sections of fresh spleen as well as on material fixed in formalin. The complete results of our studies will appear shortly in the *Folia Hæmatologica*, but at present we wish to emphasize the fact that alcohol and ether have no solvent effects upon the substance contained in the large cells. On the contrary, they produce a rather characteristic reaction and make the substance more prominent. No appreciable differences in staining reactions between frozen sections of fresh or formalin-fixed material and the material embedded in celloidin are seen, indicating that the substance remains in the cells after embedding. For these reasons we have considered that this substance may be of protein nature. Sudan III, Scharlach R, Nile blue, neutral red, and osmic acid were all negative, as well as the methods of Smith-Dietrich, Fischler, Ciaccio, and Golodetz. Weigert's myelin sheath stain was also negative, and overstaining with Weigert-Van Gieson, as suggested by Schultze, failed to show a reaction. Furthermore, no anisotropic bodies were demonstrable with the polariscope. Consequently we felt justified in stating that when neutral fats, myelin substances or anisotropic bodies are found by *microchemical methods* in the cells of any process resembling Gaucher's disease, the latter disease may be excluded.

We wish to say here that we fully realized that an appreciable amount of fats and lipoids might be present even though our microchemical tests were negative; therefore, a complete chemical analysis was made. Our results led us to believe that the substance in the cells of Gaucher's disease is not of a pure lipid nature, but of protein nature possibly in combination with the phosphatids. Any definite theory, however, in reference to the exact nature of this substance is as yet speculative.

In order to avoid any misconception regarding Niemann's case—for Drs. Knox, Wahl and Schmeisser would have us believe that their cases are of the same type—we wish to emphasize that the lesions in Niemann's case were confined to the spleen, liver and lymph nodes (the bone-marrow was not examined by them), and the histological examination showed the typical picture of Gaucher's disease. Furthermore, no reaction with Sudan III was found, the sections presenting simply a dirty, reddish tinge.

Drs. Knox, Wahl and Schmeisser also believe that the spleen described by Schultze in his case of diabetes accompanied by lipidemia is like those found in their cases, and consider it very probable that Schultze's case "represents an earlier stage in the same process." It may be stated that Schultze's case bears no resemblance whatever to Gaucher's disease. It was a case of diabetes mellitus associated with large cell hyperplasia of the spleen, the cells showing certain reactions for lipoids. Such a comparison, therefore, is of no importance in corroboration of the diagnosis of Gaucher's disease.

Since Schultze's presentation at the meeting of the German Pathological Society, two cases of diabetes of similar nature were reported by Lutz, and through the kindness of Drs. Williams and Dresbach we have recently had an opportunity of studying the material of another case of diabetes, in which large swollen reticular cells filled with fat, lipoids and cholesterol esters were found. The histo-pathology, however, was not that of Gaucher's disease.

Drs. Knox, Wahl and Schmeisser make the following statement: "Schultze showed that the sections of the spleen of his case reacted to the microchemical tests for fats and lipoids just as did the sections of the generally accepted cases of Gaucher's disease described by Risel and Schlagenhauer." This statement is not in accordance with the facts, for fats and lipoids were not present in the latter cases. In Risel's paper, on page 254, we find the following: "Dass diese Substanz nicht fettartig ist, geht aus dem Fehlen einer Schwarzfärbung durch Osmiumsäure hervor, ebensowenig färbt sie sich auch rot bei Behandlung mit Sudan III"; and also, "Bei der Untersuchung im polarisierten Lichte lassen die Zellkörper keine Doppelbrechung erkennen (weder im frischen Zustande noch nach Fixierung in Formol)." On page 129 of Schlagenhauer's article we read: "Spezifische Färbungen auf Amyloid und Fett sind negativ. Doppelbrechende Substanzen sind nicht nachweisbar." Schultze studied the slides from the cases of Risel and Schlagenhauer and noted certain resemblances to his case in the staining reactions, but he makes no mention of having examined their material for fats and lipoids. Schultze assumes, nevertheless, that there is a possibility of some lipid substance in the cells. This assumption on his part is, of course, entirely unwarranted, as we have shown.

Let us turn for a moment to the question of cellular hyperplasia in general. The literature of the past few years contains quite a number of references to this subject, clinical as well as experimental. It is well known, for instance, that certain specific cells may react to the presence of toxins in the blood and give rise to hyperplastic and proliferative changes, such as are found in typhoid fever or tuberculosis. The injection of foreign substances into the circulation in vital staining also produces a reaction of the reticulo-endothelial cells, as was shown by Aschoff and Kiyono. The feeding of animals with fatty substances or cholesterol, as was shown by Anitschkow and others, is also followed by definite cellular changes in the same specific group of cells. In fact, the histological picture produced in these experiments is so significant that Aschoff has called the process "pseudo-Gaucher." We have seen that the

lipoidemia of diabetes may cause cellular changes in the spleen somewhat similar to those described in Gaucher's disease. Notwithstanding a certain similarity in all of these conditions from the biological and histological standpoints, the nature of the process, as well as of the substance contained in the cells, differs in each instance and depends on the underlying etiological factors.

Are we then to call every morbid process accompanied by the presence of "large cells" Gaucher's disease? Drs. Knox, Wahl and Schmeisser would have us do so, provided the cells contain lipoids, for they say: "Apparently any disease in which the spleen, together with any other organ, shows numerous large, pale granular or finely vacuolated cells, giving the characteristic microchemical reactions for lipoids and showing a tendency to be widely distributed, belong to this group, and any attempt to limit the condition to any single organ or any single set of organs is largely arbitrary."

It would be presumptive on our part to suggest the proper classification of the two unusual cases reported by Drs. Knox, Wahl and Schmeisser. That a widespread cellular hyperplasia, associated with degenerative changes in many organs, exists, cannot be denied. We are unable to suggest the etiological factors, toxic or metabolic, which have produced this unique condition, but we do insist that the cases are not to be classified with a well recognized disease, definite in its clinical manifestations and always accompanied by characteristic changes in a specific group of cells.

We have shown the many points of variance in the cases reported by Drs. Knox, Wahl and Schmeisser, when compared with Gaucher's disease. These authors, in attempting to classify their cases as instances of Gaucher's disease, have built up a theory, assuming some "lipoid metamorphosis," a theory which is not substantiated by scientific facts.

ADDENDUM.

Since the above was written, a paper by Drs. Wahl and Richardson has appeared in *The Archives of Internal Medicine*, Vol. XVII, Feb., 1916, entitled: "A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant." The spleen and liver of Case I

reported by Drs. Knox, Wahl and Schmeisser were employed for this work.

We wish to emphasize that Drs. Wahl and Richardson have misquoted certain fundamental facts, and their diagnosis and conception of Gaucher's disease, being built upon these misquoted premises, are necessarily erroneous.

In the first place, there is no authentic case of Gaucher's disease in the literature in which microchemical tests for lipoids have been definitely positive. On page 239 they say: "Marchand was the first to note the presence of a peculiar homogeneous substance within the cells which is dissolved in alcohol." We wish to say that nothing can be found in Marchand's article concerning the solubility of this substance.

Secondly, we are told on page 240 that both Schultze and Lutz found lipoids in the material from the cases of Gaucher's disease reported by Risel, Schlagenhauser, and De Jong and Van Heukelom. This statement is not in accordance with the facts, for Schultze did not examine this material for lipoids, but simply called attention to the morphological resemblance of the cells in his case of diabetes to the cells of Gaucher's disease in the cases of Risel and Schlagenhauser. Furthermore, Lutz, as well, called attention to the histological resemblance of the two conditions, but was unable to demonstrate the presence of lipoids in material from Schlagenhauser's case. And, finally, neither Schultze nor Lutz made any microchemical tests on the material from the case of Gaucher's disease reported by De Jong and Van Heukelom. The latter authors, moreover, state that no fat, glycogen, amyloid or fibrin could be demonstrated in their case.

The present status of our knowledge of the chemistry of Gaucher's disease is too meager to warrant any lengthy discussion. An analysis of the figures presented by Drs. Wahl and Richardson shows that three different determinations were made on the same material with variations of more than four hundred per cent in their results. It is obvious that wrong conclusions will be arrived at if one averages, for instance, the figures of 2.5 per cent and 11.3 per cent on the same material.

We fail to see the justification of calling the acetone-insoluble portion of the extract "leicithin," without control nitrogen and phosphorus determinations.

We should like to call attention to the fact that Drs. Wahl and Richardson found a high percentage of total extractives in their case. A high percentage of extractives was also found by us in two cases of Gaucher's disease, but it is quite obvious that such findings may occur in the spleen in many pathological conditions. We do not think, therefore, that one is warranted in drawing any further conclusions from the chemical analyses reported by Drs. Wahl and Richardson.

THE RÔLE OF CERTAIN FLORENTINES IN THE HISTORY OF ANATOMY, ARTISTIC AND PRACTICAL.*

By EDWARD C. STREETER, M. D., Boston, Mass.

If among the cities of Italy Florence holds merely secondary rank as a medical center, or terrain, for anatomical studies, during the Renaissance, at any rate, the supreme achievements of her artists in the related realm of artistic anatomy more than made amends. Here she exerted a potent influence. The swift revolution in art resulting from the scientific studies of perspective and anatomy was largely

the work of the Florentine "aurifabers" and artists. The typical Florentine man of temperament was a half baked scientist; consequently, if he was also an artist, he spent much of his energy in perfecting his art on its formal side. He was a student with high and unquenchable appetencies, ready to use all the geometry that he could muster in solving problems of space, and all the anatomy that he could master in solving the problem of form. He mixed brains with his paints. Color was not his concern, but versimilitude. He would sacrifice, at any juncture, grace and sentiment for correctness

* Read before The Johns Hopkins Hospital Historical Club, December 13, 1915.

vitality. His aim was utter fidelity to fact—in a word, realism. Now, a realist who recognizes in the use of the human form the supreme decorative principle may not necessarily be an adept in anatomy, but he will be an apt pupil. He will confess at once, that only by approaching mass beneath contour can we come to apprehend the human figure in its great outlines, the scale of parts, the mutually sustained mechanism. Anatomize you must—there is no alternative. To convey reality and a heightened sense of firm substance, dissection is the only way open to the serious man working, in the figurative arts, upon problems of the human form in movement. Roundness and undulation of body surfaces, certain characters of form and texture, it is true, may be conveyed without a deepgoing knowledge of anatomy, but bodily action introduces a whole train of vital plastic complexities into the problem. Now, by the fourteenth century the Florentine figure artist was ready to cope with these difficulties. He simply had to cope with them. Before Giotto, the medieval Italo-Byzantine conventions required no knowledge of anatomy—all was flat, archaic decoration, submissive to outworn formulae: there was no need here of applying myologic detail or mechanistic interpretation. But it is quite another matter when the great figurative arts bend to the task of portraying high emotional experience. To invest tense thought with sensible shape, to stimulate the moral will of the beholder, in fact, to tell a moving story convincingly and well in a representative form, at once religious and dramatic, required of the plastic artist that he unfailingly possess all that his forerunners had acquired in the knowledge of processes and materials, and that he keep abreast of his time in subjects such as the chemistry of colors, the mathematics of composition, the geometry of perspective, the illusions of chiaroscuro, and, above all, the science of human anatomy.

Provided he is well drilled in these disciplines, the artist has it in his power, in his very hand, to create a world of sensuous delightfulness framed for the spiritual uses of his kind. He *may* invest religious emotion with esthetic charm. He *must*, absolutely *must*, satisfy the imperious demands of secular art in the matter of faultless drawing and modeling of the undraped human form. From Masolino on, negligent drawing of the figure was a crime no maestro would be guilty of.

Dwell just for a moment upon certain incentives to the adoption of forms of art, frankly naturalistic, first observable in Florence in the fourteenth century. What social, civic or economic conditions gave to art on the Arno the specific direction of which we speak? Well, first of all, the new art was bourgeois by birth, and its appeal to the bourgeoisie must be fresh, simple, and immediate. It spoke unvarnished truth. It must avoid the region of abstractions and mystical conceptions, and cleave to the ponderable and measurable objects of sight and sense. In the second place, your realist directs his appeal to the honest, honorable intelligence of his fellows. He is close to their farthest-darting apprehension of the world of sense. Thus he becomes the protagonist of science, a self-appointed discoverer of truth. He is the first to feel the quickening to life of new faculties, of fresh intellectual interests, in his own

milieu and time. He is a snapper-up of innovations, always on the alert for some novel way of illuminating the old substance of religious feeling. Symonds has something on this head:

As technical skill increased, and as beauty, the proper end of art, became more rightly understood, the painters found that their craft was worthy of being made an end in itself, and that the actualities of life observed around them had claims upon their genius no less weighty than dogmatic mysteries. The subjects they had striven at first to realize with all simplicity now became little better than vehicles for the display of sensuous beauty, science, and mundane pageantry. The human body received separate and independent study, as a thing in itself incomparably beautiful, commanding more powerful emotions by its magic than aught else that sways the soul.

Now, Art and Science during the Renaissance, "like two stars that held their motion in one sphere," kept trailing each other curiously. Particularly was this true in Florence, where the Medici encouraged all the scientific tendencies of Tuscan art. We have seen that the true creative power of the Florentine artist lay almost wholly on the formal side of his art. With the deepening of his scientific interests he applied himself with more fervent industry to the study of the technicalities of his craft. He appropriated inherited forms of expression more rapidly, and created new ones more readily. Always drawing was his chief concern—good realistic narrators and very few painters, in the strict sense of the word, came of Florentine blood. It is characteristic of him to make form alone serve as the living vehicle of the artistic idea. Indeed, he fashions his very ideas plastically. He uses his drawing pen, his modeler's stick, his chisel, casting-mould and chasing-tool, like so many instruments of precision: it is a foregone conclusion that he will use the dissecting knife, too, in the same service. The which he does.

I fear our notion of old Florence is somewhat jejune in one respect. We picture the city as an aggregation of deep gardens, and courtly precincts, all peopled with exquisites, whose discourse is neo-platonic nebulosity. The princes, the poets, the humanists are held too high in our evaluation. As a matter of fact, this city is the very paradise of little bank clerks who compose, not amorous rondels, but solid works on mercantile arithmetic; sound craftsmen who measure, balance, calculate, explore, just as Dante did, just as Giotto, Dante's friend, did, too, in his rude way. In Giotto are found the seeds of all future development of art in Florence—intimations of a vast abortive inquiry into the physical makeup of man, among other things. Among his followers is found still more curious research in this unblest quarter. His intimate (some say his kinsman), his intimate assistant Stefano is called "the ape of Nature." Billi tells us that this Stefano attained such a pitch of realism in drawing the human figure that the barber-surgeons, preparing to do a phlebotomy, would stand before his subjects and study the detail of the branching of the veins of the arms. His period is 1301-1350.

Reorganization of the study of nature was the issue of Giotto's teaching. The artistic training of a fourteenth century Italian "Primitive" was not so haphazard as we are

led to believe. Glance for a moment at the "Treatise on Painting," by a pupil of a pupil of Giotto—Cennino Cennini is his name, and he lived at the end of the fourteenth century. In Chapter 70, part 3, he says, speaking of the proportions of the human figure: "I will make you acquainted with the proportions of a man; I omit those of a woman because there is not one of them perfectly proportioned." A rude beginning and a rude treatise, but it is the best since Vitruvius. "Flesh tints," continues Cennini, "are laid on with verde terra and biacca; go twice over the naked parts. When painting the faces of young persons with fresh complexions this tint should be tempered with the yolk of a town-laid egg. . . . You must prepare three gradations of flesh color. . . . Now we will speak of coloring a dead man; that is to say, his face, his body, or any naked part that is visible. Use no rosy tints, because dead persons have no color; add a little light ochre; mark the outlines with sinopia, mixed with a little black, which is called sanguine. But, I warn you, use no color which you have not seen. . . . When you have to paint the bones of Christians make them of the flesh color ('incarnazione'). Having to paint a wounded person, you must lay a tint of pure cinnabar wherever the blood is to appear; then glaze this and the drops of blood with fine lake, tempered in the usual manner."

In subsequent chapters he describes methods of taking a life-cast of the face, casts of the entire figure, of a man, a woman, or an animal; how to model from life, etc. And so through the whole gamut of that earlier practice among the Giottoeschi. Parenthetically, I would say that all the great technical treatises on the science of perspective and the science of bodily proportion, except Dürer's, issued from Florence; Ghiberti, Alberti, Leonardo, Michaelangelo, Rosso de Rossi, and you may add the work of Luca Paciolo, "Divina Proportione." Likewise, in the great outpouring of mathematical works, between the years 1472 and 1500, Florence had her full share (213 mathematical treatises were printed in Italy in those 27 years, 100 of these issuing from press between 1480-1490). The Florentine artists were, many of them, gifted mathematicians; this is very true of Brunelleschi and his pupils. Vasari says of Verrocchio, "In his youth Andrea gave considerable attention to science, more especially to geometry; Ucello likewise." Of Piero della Francesca, Vasari says: "He understood all the most important properties of rectilinear bodies better than any other geometrician." The greatest mathematical compiler in all Italy, Luca Paciolo, received his training from this same Piero della Francesca, as well as later assistance from Leonardo. Da Vinci himself was a mathematical genius of the purest ray. "Let no man read me who is not a mathematician. No human investigation can lay claim to being true science unless it can stand the test of mathematical demonstration. The man who undervalues mathematics nourishes himself upon confusion. The more mathematics, the more science." A recurring phrase in Leonardo's manuscripts is "la somma certezza della matematica" (the apodictic certainty of mathematics). Certainly the science of quantity had gained a great exponent and protestant in Leonardo, for he was one who was ready to place

his transcendent talent as an artist at the disposal of pure science—almost without reserve.

I have digressed so far only to prove again to you that we here are dealing with unabashed scientists of the brush. Leonardo is merely the end-result of uncompromising realism. His passion for research is the outcome of Verrocchio's method. His master, Verrocchio, was taught by Baldovinetti, who in turn derived from Domenico Veneziano, who in turn derived from Andrea del Castagno. The last named, by the way, is described by a contemporary as "amatore della difficultà del arte." There was no attempt at evasion of the natural difficulties encountered by the representative arts at Florence after the coming of this man Andrea "of the hung." The scientific impulse found firm lodgment in him. It seems as though the desire were stronger in him than in his fellows to rid himself at once of elusive and symbolic half-statement and gain a share ever greater in the divine truth of form. He is not one to be easily put off with the elementary rules of bodily proportion. He is bitten with *corporum intus curiositas*. He will take all the hazards of his art, will descend to the charnel-house under the New St. Mary's Hospital and make assay of the "Science of the Sepulchre." In fact, he painted a figure of Saint Andrea "beneath the charnel-house in the cemetery of Santa Maria Nuova," adds Vasari; and he gave such solidity of form to his patron saint that the superintendent of the hospital had him decorate a part of the principal chapel of the church above (1450-52). Domenico Veneziano and Baldovinetti, master and pupil, both first-rate exponents of the new art, were at work there—but I anticipate. Leonardo says that Andrea drew his muscles so boldly that his figures looked like bags of nuts. This was true of his drawings only, not of his painted subjects. Exaggerated myologic detail is constantly met with among the sketches of the early Florentine painters. So it is among their pen and chalk drawings that we find strongest evidence of a taste for anatomy among these masters. Certainly Castagno had such a taste to a degree! He did not rest content with his knowledge of the superficialities of structure. The unclouded drawing of the human figure in action required that he plunge into the complexities of his subject. The muscles, situated immediately under the skin, interest him primarily, but the joints and the skeletal mechanism under the operation of the muscle-groups is a matter of profounder moment to him. Certain aspects of the artist's *problem of form* are speeding on the way to resolution, under guidance of this man. It looks as though Castagno is under some grim bond to naturalism, whereby he engages to trace no outline that does not express his personal knowledge. Whatsoever his miniver brush relates, he has experienced. The muscles which he draws so boldly are solidly attached to actual underlying skeletal parts, and are capable of putting solid members into action. Because he cannot render tip-toe movement and the grace of life, he fails to please Mr. Ruskin. Not that that matters in the least! The thing to note is Andrea's attempt at an utter fidelity to fact, his portraiture of the body as well as the face, his forthright draughtmanship—these he got through anatomies.

The manner in which he arrived at a point of serene power, and vastly influenced the Florentine school, is precisely the manner of Leonardo. "Study the science first; then follow the practice." Better teaching was at hand, perhaps, in Umbria; yet Tuscany proceeded to follow Castagno. He greatly influenced Pollaiuolo and Botticelli, and to a lesser degree Doménico Veneziano who, I repeat, taught Baldovinetti, who taught Verrocchio, who taught Leonardo. Thus the scientific mantle of Castagno passed down in a line of direct descent to Leonardo. These men no longer studied intensively the nudes of Masaccio in those epochal frescoes flanking the Brancacci Chapel at the Carmine—I mean "Peter Baptizing," or "The Expulsion from Eden"; nor did they travel to Castiglione d'Olena, to view Masolino's "Baptism of Christ." They still regarded these pictures as sheer miracles of unimagined power of drawing—precious testimony from the founders of an art that henceforth was to be grounded not upon intuition but upon perception and knowledge.

I pass to Paolo Ucello. In Paolo Ucello we have an awful example of an artist whose zeal for the house of science "hath eaten him up." He had an over-freight of scientific interest. Of adventurous mental temperament, he went squarely to the attack on all the laws governing perspective. As he died in 1475, three years before the first book on practical arithmetic was printed, we may conceive of his difficulties. He turned to Giovanni Manetti for help. "With this philosopher," says Vasari, "Paolo conferred very frequently, and held continual discourse concerning"—what? The formulae of art? No. "the problems of Euclid." Donatello, pleading possibly in behalf of the neglected wife of the poor science-smitten man, once expostulated with him: "Ah, Paolo, with this perspective of thine, thou art leaving the substance for the shadow." For his own private worship Paolo painted five panels in his bedroom representing his five heroes—Giotto, in painting; Brunelleschi, in architecture; Donatello, for sculpture; himself, for perspective; Giovanni Manetti, for mathematics. Ucello is truly to be counted a hero—his self-sacrificing labors enabled later painters to proceed from a basis of exact science to the far nobler pursuit of ideal beauty. Those scores of unknown industrial craftsmen like him, in Florence, everywhere eager to impoverish themselves and render up their lives for science, were smoothing the way for our Leonardo.

Much could be said about Donatello. To him, as to any worker "in the round," bred to the processes of sculpture and metal-shaping, bone and brawn construction was the paramount interest. He modeled the body as he modeled the head, in a spirit of uncompromising portraiture—to embellish is to falsify. He expresses his hatred of simulacra, in every touch of chaser and chisel. To prove that Donatello assisted at anatomies, at least from the spectators' bench, we have the sole evidence of that Paduan bronze tablet representing "The Anatomy of the Miser's Heart" in the series of Miracles of St. Anthony. You will recall that the forceful rendering of the human form, the muscular litheness and movement of Donatello's work, were the especial admiration of Michaelangelo, and helped mightily to form him. Donatello's bronze "David"

at the Bargello is the first nude statue of the Renaissance. (It is interesting to note that the first mention of practical school-anatomies at the Florentine University coincides with Donatello's birth-date.)

The "Statuta universitatis et studii Florentini," under the date 1387, deal with dissection of bodies at the school, under six explicit heads, specifying the duties of the Rector and Beadle; the delivery of the bodies by the officers of the Podestà; the crying of the anatomy through the school precincts; the choosing of a responsible student whose quarters are large enough to admit the chosen advanced students who pay and the few readers and the Rector who do not pay; the careful accounting of the costs—the fees to the porters and to those who say mass over the body and bury it, as well as the cost of the good cup of wine given to brace each quasi-valiant heart before and after the ordeal. "In case God grants the Studio to grow, then let the Podestà see to the delivery of not two but three bodies of alien criminals each year; whatever their foul felonies be, let them be hanged (not burned as the wont is with witches, nor beheaded) and delivered the same day, for corruption comes on apace."

Now, an artist rarely saw such a school-anatomy in Florence—the audience was strictly limited in ways that would naturally exclude him, unless he was a friend of the Rector. However, there were three ways open to him to appease his "corporum intus curiositas": (1) To wait for a public dissection (which occurred at unconscionably long intervals); (2) to go to private dissections performed by his doctor friends; (3) to make up little post-mortem parties of his own. Almost invariably would he choose the third method. He went or sent to the gibbet, or to the newly laid grave, if a poor man; if a man of repute and in good odor with the brethren, he could work in the dead-house of the hospitals. I dare say the large majority of Leonardo's dissections were done in the hospitals of Florence, Milan and Rome. Michaelangelo did his anatomies in lordly style—hired a house in the St. Agata quarter and got Realduo Columbus to ship him subjects. Michaelangelo's pupil and chief assistant in the Medicean tombs, Montorsoli (who probably did the figures of Cosimo and Damian flanking the monument), worked even more intimately with the anatomists of the schools (Genoa). There is rivalry, almost bitter at times, between the anatomizing artists and the practical anatomists. Hear what Condivi has to say here (Condivi is the pupil and biographer of Michaelangelo): "From a child Michaelangelo was a hard worker, and to the gifts of nature added study, not using the labor and industry of others, but desiring to learn from nature herself; he set her up before him as the true example. There is no animal whose anatomy he did not desire to study, *much more, that of man*, so that those who have spent all their lives in that science, and who make a profession of it, hardly know so much of it as he. I speak of such knowledge as is necessary to the arts of painting and sculpture, not of other minutiae that anatomists observe." So much from the artistic camp—now the other side. Vesalius, on page 115 of the work on China root, says that he anatomized a Florentine patrician, Prosper Martellus; and then a few

pages later comes this very curious outburst: "As for those painters and sculptors who flocked around me at my dissections, I never allowed myself to get worked up about them to the point of feeling that I was less favored than these men, for all their superior airs."

Now to return to the age of Donatello. There is a largeness of intelligence, a quickness of sympathy, a god-like comprehension in men of the stamp of Ghiberti, Brunelleschi, Donatello, della Robbia. They were many-sided, like Orcagna, possessed of eight souls. The task of the revival called for men of amplest powers. Florence contributed men distinguished for their peculiarly versatile genius and the vast variety of their acquirements. The qualities of daring, variety, and brisk vigor are found (as in one of the pupils of Ucello and Donatello, Antonio Pollaiuolo) sometimes disassociated from breadth of vision, elevation of feeling, and human sympathy. However, as Pollaiuolo was "the first Florentine master to study human anatomy systematically in the modern sense," he will serve to bring our loose account to the tightening point. Born in 1429, the grandson of a poulterer, apprenticed to Ucello, then to Donatello, for whose cruel naturalism he had a keen taste, we see him moving along paths of detailed, severely accurate, technique, in niello engraving and in the casting of little bronzes. He is painter, sculptor and jeweler, too. Pretty soon we see him moving along paths more elaborate, of purely objective scientific inquiry, in quest of the intimacies of form; and, with a goldsmith's regard for detail and fineness of handling, he begins to anatomize. "He dissected many human bodies," says Vasari, "to study the anatomy, and was the first to investigate the action of the muscles in this manner, that he might afterwards give them their due place and effect in his works." Ruskin has something injurious to say anent this; I quote: "The virtual beginner of artistic anatomy in Italy was a man called the 'Poulterer,' from his grandfather's trade; Pollaiuolo, a man of immense power, but on whom the curse of the Italian mind in this age was set at the deepest. . . . Pollaiuolo, Castagno, Mantegna, Leonardo da Vinci, Michaelangelo, polluted their work with the science of the sepulchre and degraded it with presumptuous and paltry technical skill. . . . Foreshorten your Christ, and paint him, if you can, half putrefied—that is the scientific art of the Renaissance." This occurs in a note to "Ariadne Florentina." It is a note that does not require any answer. Some day let us learn to shun the frumious Ruskin as we would the bandersnatch: when he is raw and intemperate, and turbid and fallacious, at least then, let us not go down in craven submission to him. At any rate, Pollaiuolo got at the mainsprings of bodily movement; he recorded his progress in anatomy in a model series of drawings, full of "bizarre energy," which were eagerly passed around among the artists of his day. These drawings reveal him, as Berenson declares (in his "Drawings of the Florentine Painters"), as "one of the greatest masters of movement that there ever has been; one of the ablest interpreters of the human body as a vehicle of life-communicating energy and exulting power." His influence was as great as it was bracing. He even influenced Germany through Dürer. He affected all schools, all sorts and condi-

tions of artists, Botticelli, Signorelli, Piero di Cosimo, possibly Verrocchio, to whom I now turn.

Like "the Poulterer," Andrea del Verrocchio was a pupil of Donatello. He was a goldsmith and general art entrepreneur, of highest renown as a teacher of painters. As a sculptor he was the best between Donatello and Michaelangelo. His great bronze equestrian statue of Colleone will mark him as "ganz apart." Like a colossus he bestrode the crews of bronze-casters in Florence, who were turning out objects for household decoration. He was the very man to inspire the young Leonardo, a supreme technician, whose work was finished *ad unguem*; a scholar, whose devotion to the mathematical disciplines I have already dwelt upon. Vasari says that he possessed two drawings by Verrocchio "of two horses with various measurements, and the proportions according to which they are to be increased from a smaller to a larger size—all of which are correct and free from error." In the bronzes of Verrocchio, and in his panels and drawings, searching anatomic features can be noted; and if we can entirely trust Mathias Duval (who after all is an authority in the matter), there also exist certain *écorchés* or flayed figures, purely anatomical in purport, which were used in Verrocchio's "Bottega" and were fashioned by him for the use of his pupils.

There is no doubt as to anatomy being a part of the established curriculum in the Florentine "Bottega" from now on. Men from remote schools came to steep themselves again in Florentine science. Piero della Francesca, and his heavenly appointed spiritual heir, Signorelli, came from Umbria wanting to draw "the nude, the whole nude and nothing but the nude."

There are increasing evidences of an easy intimacy between artists and physicians. Both Piero della Francesca and Ridolfo Ghirlandaio painted a "donna gravida," and we have an occasional scene in a medical ward (Domenico di Bartolo at Sienna), an interior of a bathing establishment (Franciabiagio), a sepulchral monument (Verrocchio Tornabuoni). Bernardo Rossellino did a fine portrait bust of the physician Giovanni da San Miniato, signed, and dated 1456 (now in South Kensington). Office consultations are found, in miniatures in manuscripts, and also the well-known low relief by Andrea Pisano on the campanile of Santa Maria del Fiore. It is called *Medicina* and is second in the series of mechanical arts. The scene is a consulting room; the surgeon is seated to the right, in a cathedra, urine-casting; next him, his assistant holding a mandrâgora plant in his left hand and rudely pointing with his right thumb to a gravid young woman standing at his right. Near the door are two women carrying urinal baskets. Of course, out of flattery to Cosimo de' Medici, Florence, from early days, was flooded with representations of the healing saints Cosimo and Damian, in fresco, oil and marble. Hygeia with her serpent is one of the archaic details of the Mandoria portal of the Duomo.

Everywhere throughout the city you will meet with hints of primitive, as well as present, correspondencies between the plastic arts and medicine. The painter Cosimo Roselli, founder

of a school marked by enthusiasm for studies anatomical, should never have become an artist at all, but a physician; for it was his family that had kept the immemorial "Lily Pharmacy" hard by New St. Mary's Hospital. How these easy intimacies arose between physic and the figurative arts would be hard to explain in any other way than the one I shall attempt to use, simple and obvious as it is! It was by the hazard of association in one and the same guild that the anatomists and artists of Florence made their magnetic contacts. The painters formed a sub-membrum of the "Guild of Physicians and Apothecaries." They all belonged—Giotto, Masaccio, Castagno, Uccello, Verrocchio—to the membrum pictorum of the Guild of Physicians and Apothecaries. Masaccio joined the guild first as an apothecary (in 1421, at the age of 19); then he matriculated under the membrum pictorum (in 1423). You see, the apothecaries included color handlers, the "spetiarii, qui emunt, vendunt et operant colores et alia ad membrum pictorum spectantia memoratum" (apothecaries who buy, sell and deal in colors and other materials needed by the artists). By virtue of this affiliation the artists and doctors were thrown together in all the multifarious guild functions; they sat together in the guild Council; walked together under the same banner in pageants. It cannot, therefore, be a matter of surprise to learn that Giotto was the friend of Dino del Garbo and Torrigiana, or that Luca della Robbia (almost 200 years later) was

a friend of the founder of pathological anatomy, Benivieni, although the latter was almost half a century (49 years) younger than Luca. (Luca, you will recall, executed the great arms of the Guild of Physicians, a polychrome terra cotta medallion in Or San Michele.)

The opening chapter of artistic anatomic studies at Florence, ending with an account of Verrocchio, furnishes us with only a meagre amount of good provable and usable material as compared with the account of Leonardo or Michaelangelo and their followers. With Leonardo, of course, would be grouped Lorenzo di Credi, de Predis, Boltraffio, Sodoma, and Melzi who was custodian of his scientific manuscripts. Michaelangelo's group would be large and difficult to handle, but we would single out Montorsoli and Sebastian del Piombo. There is yet another group to be studied, *i. e.*, Cosimo Roselli, Piero di Cosimo, his pupil, Andrea del Sarto, his pupil in turn, and the entire school of del Sarto (which was under the influence of Michaelangelo), Pontormo, Franciabiago, Rosso Fiorentino.

And to that immortal ruffian, Benvenuto Cellini, who in his diary sums up the tale by remarking that the "essential thing in art is thoroughly to understand how to paint the nude," to him separate space might be given, as to one, somewhat isolated from the moral order, but within the pale of an Art that was still in the midst of her traffickings with Science.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

DECEMBER 6, 1915.

1. Report of Cases: Chloroma and Acute Myeloid Leukemia. DR. JOHN T. KING, JR.

To appear in full in a later number of the BULLETIN.

2. Chemical Studies in Bichloride Poisoning. DR. D. S. LEWIS and DR. T. M. RIVERS.

To appear in full in a later issue of the BULLETIN.

3. Experiences with the Epidemic of Typhus Fever in Serbia. DR. R. P. STRONG.

To appear in full in a later issue of the BULLETIN.

DECEMBER 20, 1915.

1. Spontaneous and Experimental Leukemia of the Fowl.* (Abstract.) DR. H. C. SCHMEISSER.

In this paper was presented the first unit of an extensive study of a transmissible leukemia of the fowl.

Careful examination of a case of spontaneous leukemia of the fowl showed this to confirm in every detail the findings of Butterfield, Mohler, Warthin, Kon, Soshestrenski, Ellermann and Bang, Hirschfeld and Jacoby, and Burckhardt. The blood and anatomical findings closely simulated those of human myeloid leukemia.

By intravenous and intraperitoneal injection of an organic emulsion from this bird the disease was produced in 13 previously healthy fowls, and carried into the fifth generation, giving a blood

and anatomical picture identical with that of the spontaneous case, and a clinical and anatomical complex which is analogous to that in the human disease. This is in confirmation of the work of Ellermann and Bang, who first successfully transmitted the leukemia of the fowl.

DISCUSSION.

DR. W. A. BAETJER: I have been much interested in this same subject from the standpoint of human leukemia, where of course no one has been able to progress anything like so far as Dr. Schmeisser has been able to go in the study of fowls. It seems to me that Dr. Schmeisser has opened up the possibility of solving the problems of this disease, which may be of great aid in studying the leukemia of man. It comes at a most interesting time with relation to human leukemia in the sense that there have been, for the past two years particularly, an increasing number of reports which have seemed to suggest the possibility that at least some cases of human leukemia are of an infectious nature. I presume from what Dr. Schmeisser has said that he regards this disease of fowls as being infectious rather than neoplastic. Most of the evidence in the human cases, it seems to us at least, is distinctly in favor of the same conclusion. In that sense it throws a great deal of light on human leukemia and comes at a time when most of those who are working have held back from stating whether they think it is an infection or not. In the last two years, at least three cases have been reported in which an organism has been isolated from the spleen or glands of patients. But in no case have investigators been able to reproduce the disease with these organisms, nor has it been possible in any way to reproduce the typical disease, as Dr. Schmeisser and others have done with the fowl. It seems to me, then, that this offers a very definite advance from the standpoint of human leukemia, in that

* Published in detail in the *Journal of Experimental Medicine*, 1915, XXII, 820-838, and fully illustrated in The Johns Hopkins Hospital Reports, 1916, XVII.

you can get in the fowl a picture that is clinically and pathologically similar to that of human leukemia, but which differs from it, in that it has been transmitted from animal to animal by means of tissue inoculations. No one can doubt, I think, that it corresponds in most ways to human leukemia. That it is the same disease, I think is still somewhat open to doubt, because human leukemia presents at the present time a very mixed picture. There are cases which correspond with the cases Dr. Schmeisser has reported in the fowl. Others do not, from the standpoint of blood examination, from the clinical course or from pathological findings. Dr. Schmeisser has brought out that you can have an aleukemic stage coming on in the same series of animals. In aleukemia the picture is interesting at the present time in connection with the efforts on the part of many to put such diseases as Hodgkin's disease and certain other obscure glandular enlargements into the class of leukemia.

The most interesting feature of the paper is the evidence it offers that a disease which simulates certain types of leukemia in the human being occurs in the fowl, and that in the fowl the disease is definitely infectious. This point gives us far more to go on than we have ever had in dealing with human leukemia in regard to its etiology.

I should like to ask Dr. Schmeisser with regard to the pathology of leukemia, whether he feels that it is a very distinct and specific type of change; i. e., whether the pathology of leukemia in general, acute and chronic, is specific. I should like to ask also whether, from what he has seen in his slides, he could offer any conclusive evidence on a point which has caused a good deal of confusion in human pathology, namely, whether the enlargement of the spleen in human leukemia is the result of an infiltration with the same cells which circulate in the blood, or whether it is due to what is termed a myeloid metaplasia?

DR. S. R. MILLER: I should like to know Dr. Schmeisser's basis for calling structures blood platelets which are larger in size than red blood cells and which contain protoplasm and dividing nuclei.

DR. SCHMEISSER: In answer to Dr. Baetjer's questions: (1) Typical cases of both lymphoid and myeloid leukemia produce pathological pictures which are specific. (2) Whether the presence of the myeloid cells in organs and tissues outside of the bone marrow in leukemia is due to an infiltration and proliferation of the same or due to their origin *in loco* by a reversion of the vascular endothelium to its embryonic hematopoietic function and then a proliferation, I am not at the present time able to offer any conclusive evidence.

In answer to Dr. Miller's question: The structures referred to were called blood platelets simply as a means of classification and not because they are known to be analogous to the human blood platelet.

2. The Quantitative Study of Analgesia after Opium Alkaloids.

Drs. D. I. MACHT, N. B. HERMAN and C. S. LEVY.

A preliminary communication on the subject was published in the proceedings of the *National Academy of Sciences* for December, 1915; and the complete paper appears in the *Journal of Pharmacology and Experimental Therapeutics* for January, 1916.

3. The Action of Papaverin on the Ureter. (Abstract.) Drs. D. I. MACHT and J. T. GERAGHTY.

DR. MACHT: In connection with the preceding paper I wish to report a few experiments performed by me within the last few weeks, in order that the same may be recorded in the minutes of this meeting. I have already called attention to the general analgesia produced to some extent by injections of papaverin. This rare alkaloid of opium possesses a number of very interesting properties. I have already shown in the *Journal of Pharmacology and Experimental Therapeutics* for September, 1915, its action upon the respiratory center, and have also called attention to its

stimulating effect upon the heart and to its interesting action on the coronary circulation in the *Journal of the American Medical Association*, May 1, 1915.

Perhaps the most interesting property of this drug is the one to which attention has been called by Pal of Vienna and his co-workers Popper and Franckel. These authors point out that papaverin lowers the tonus of all organs composed of smooth muscle. I have been able to confirm their results by personal observations on isolated arteries, uterine strips and intestinal muscle.

Very recently I have had the opportunity of studying, together with Dr. Geraghty, a patient suffering from ureteral calculus, and the idea occurred to us to introduce a solution of papaverin through the catheter directly into the ureter, just below the stone. Knowing from my experiments that papaverin is not toxic, there was no objection to this procedure. Five cubic centimeters of a 2-per-cent solution of papaverin hydrochloride were therefore introduced. On the same afternoon the patient experienced slight colicky pains, and on subsequent examination the stone was found to have descended a considerable distance. After a second treatment with papaverin the patient spontaneously passed the calculus. Dr. Geraghty, while making the injection, could observe with his eye through the cystoscope that the ureteral orifice dilated after the introduction of the drug.

Following this experience I have performed a number of experiments on the isolated ureter of a pig. I was surprised to find that the ring of pig's ureter suspended in oxygenated Locke solution began to contract rhythmically not unlike a frog's heart. These contractions continued spontaneously for several hours at a time. On addition of 5 mg. of papaverin, and even less, there was an immediate relaxation of the ring and a discontinuance of the contractions. Exactly the same observations were made on the human ureter obtained from an operation. So far as I know, these observations have never been made before. It may be further stated that papaverin not only exercises a general analgesic effect, but also acts as a local anesthetic. Attention has been directed to this fact by Pal, and it has been confirmed by me from observations on myself and some of my colleagues.

In this connection I may as well add that even more interesting than the action of papaverin upon the ureter has been found by me to be the effect of epinephrin. The smallest amounts of this drug, I was surprised to find, increased the frequency of the ureteral contractions and markedly increased the tonus of the ureter. Indeed, even a *quiescent* ureter, that is, a ring which is almost dead and is not contracting, can be revived by the addition of a little epinephrin. A general study of the pharmacology of the ureter is now being carried on.

DISCUSSION.

DR. GERAGHTY: Theoretically, a stone which is sufficiently small to leave the pelvis of the kidney and pass into the ureter should be spontaneously expelled, because the narrowest part of the ureter is its junction with the pelvis. It has been estimated, however, that only about 75 per cent of the stones which enter the ureter are spontaneously expelled. Many of those which become impacted can be removed by manipulative procedures. About 15 or 25 per cent of the stones become arrested in the vesical portion of the ureter and practically all of these stones can be readily removed by intravesical procedures. For stones that become impacted above this point we have heretofore relied upon the passage of an ureteral catheter, with the idea of changing the position of the stone, and possibly its axis, in order to allow its shortest diameter to lie in the ureteral canal. Frequently stones are passed which have been manipulated by the ureteral catheter, even those that have been present for several years. The use of the thermocatheter seems to promise more than the use of the simple catheter, because by means of the heating we not only can

manipulate the stone, but also can secure a certain degree of dilatation.

A few months ago I had a most striking example. The patient had a stone impacted at a point 12 cm. from the vesical orifice. A special thermo-catheter was passed as far as the stone, heated to about 115° and then slowly withdrawn. When the catheter was removed from the ureter the stone was found in the vesical portion, having followed the catheter directly down.

Papaverin seems to promise considerable help, because it produces marked relaxation, but some technique will have to be devised by which we can limit the action of the papaverin to the ureter below the stone, or else secure dilatation without paralyzing completely the ureter wall. In order to expel the stone it is necessary to preserve the propelling properties of the ureteral wall itself.

In the case reported by Dr. Macht the stone was very promptly expelled following the injection, without any colic.

JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

DECEMBER 13, 1915.

1. The Rôle of Certain Florentines in the History of Anatomy, Artistic and Practical. DR. EDWARD C. STREETER.

This paper appears in full in the current issue of the BULLETIN.

DR. H. M. HURD: Just twenty-five years ago The Johns Hopkins Hospital Historical Club was organized. I suppose I am the only one here to-night who was present at its first meeting, at which Dr. Welch presided and Dr. Osler gave the first paper. Dr. Osler was very much chagrined at the form of the printed programme.

In addition to reading his paper, he had intended to have an exhibition of old books, and had numbered his talks 1 and 2. One of the books he had planned to show was John Morgan's Treatise on Education, which he had numbered 1. Unfortunately, through an error of the printers, the programme read: "1 John Morgan. By William Osler." Dr. Welch also gave a talk at that meeting, I think on books. There were not a great many present, and I am afraid we all felt the society was not destined to be very long lived. It was supposed that we should soon see all the old books we could obtain, and that then interest would naturally die out.

It is astonishing, however, how interest in the meetings of the club has been kept up and how much good work has been done. We have had papers of course not displaying any great amount of scholarship, but these have been of a character to indicate where sources of knowledge could be traced. The several papers which Dr. Billings gave us were always extremely valuable. He at one time delivered here, over a period of three or four years, a series of lectures on the history of medicine and used to appear at the meetings and discuss the questions presented. A great many of Dr. Osler's brilliant essays were read before this Historical Club, and also many of Dr. Kelly's. We have had unusual kindness shown us by scholars throughout the country, indeed I may say throughout the world. We have had papers from men whose writings and whose presence have been a great inspiration to us.

We have now begun the second quarter century of our existence. As I have said, I was present at the first meeting, and I am hopeful that I shall be present at the celebration of the second quarter century. If I cannot be, it is my wish that the society will still be in active operation.

NOTES ON NEW BOOKS.

Mechano-Therapeutics in General Practice. By G. DE SIVIETOWSKI, M.D., M. R. C. S. Cloth, \$1.50. (New York: Paul B. Hoeber, 1914.)

The author of this volume has succeeded in emphasizing the simplicity of the technic of massage. The subject is treated with unusual clearness and is singularly free from complicated and confusing description of a technic that depends upon its very simplicity for its effect.

In the chapter on "indication and contra-indication," we notice with pleasure the absence of the enthusiast. We may not agree with the author on his treatment of fractures, nor will results obtained in individual cases always be convincing; still the work should be useful to those interested in the subject. C. R. A.

Diseases of the Nose, Throat and Ear—Medical and Surgical. By WILLIAM LINCOLN BALLENGER, M.D. Fourth Edition. (Philadelphia and New York: Lea & Febiger, 1914.)

From certain points of view this is perhaps the most valuable book on this subject in the English language. On the other hand, even the thoroughly revised fourth edition is open to criticism.

Although containing over one thousand pages the book makes only a very feeble attempt to correlate the focal lesions of the nose, throat, sinuses, larynx and ears, as seen by the laryngologist and otologist, with the general manifestations as seen by the internist, the pediatrician and the neurologist.

The chapters dealing with the inner ear are the least satisfactory in this edition. To those not already familiar with the fundamental principles, the author's description would be extremely confusing, since he has not clearly distinguished between facts and hypotheses. This criticism applies particularly to the vestibular apparatus; the chapter on the functional tests of hearing is well worth reading.

The book, as it stands, will prove of great value to the specialist, but the author could have made it of equal value to the medical student and general practitioner, by emphasizing the relation of focal infections to the various general systemic disorders.

S. J. C.

Cane Sugar and Heart Disease. By ARTHUR GOULSTON, M.A., M.D. \$2.00 net. (New York: Paul B. Hoeber, 1915.)

It is to be regretted that this book should have been published before the glaring mistakes could have been called to the attention of Dr. Goulston; but then, one wonders, Would there have been anything left to publish?

The book of one hundred pages starts with sentences culled from the work of cardiac authorities that serve as a frame-work for twenty pages of highly improbable and unsatisfactory suggestions that are "conclusive" as to the value of cane sugar as a cure-all in cardiac therapy.

This conclusion is suggested by about fifty pages of cases that rival the columns in the daily papers devoted to the testimonials of patients that have been cured by twenty drops of Duffy's Malt Whisky—both in the medical knowledge portrayed, and in the satisfactory results. One is somewhat abashed at the ease with which the writer diagnoses a case of "auricular fibrillation with auricular tachycardia" by the radial tracing, and must, perforce, marvel with the author at the complete recovery by the use of cane sugar in this and other cases. But when the reader notes the development of soft vessel walls in a case of atheromatous arteries, following a year of five ounces of cane sugar daily, and the cure of a case of tuberculosis by the same therapy, he will probably smile as he closes the book. The remaining twenty pages that he misses thereby are made up of radial tracings wrongly diagnosed, an abstract from the Times on The Strain of Life in the Great Cities, and a warning that the use of beet sugar is without avail.

E. W. B.

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NITROGEN METABOLISM DURING PREGNANCY.

By KARL M. WILSON, M. D.

(From the Obstetrical Clinic, Johns Hopkins Hospital.)

During the past 25 years a number of observers have made contributions to our knowledge of some of the problems of metabolism arising in the course of a normal pregnancy, labor and the puerperium. Unfortunately, practically all of the observations upon women have been made on patients studied only for the last few weeks of the pregnancy, and in some cases only for the last few days, whereas the study of the various phases of metabolism in the early months of pregnancy has been almost wholly neglected.

Various observers have approached the subject through the study of the metabolic processes in pregnant animals. On account of the shorter duration of the pregnancy, together with the possibility of keeping the animal on a fixed diet throughout the entire period of the pregnancy, such studies are naturally more satisfactory than is the case when pregnant women are studied.

Hageman, Jägeroos, Ver Eecke and Bar have made extensive studies on the nitrogen metabolism of pregnant animals throughout the entire duration of their pregnancies. Ver Eecke used pregnant rabbits; Hageman and Jägeroos carried out their observations on pregnant dogs (the duration of the pregnancy being 60 days), whereas Bar used both rabbits and dogs, the latter proving to be much more satisfactory for purposes of study.

Hageman found that in the dog the pregnancy could be divided into two distinct metabolic periods, corresponding in time to the two halves of the pregnancy. In the first, the animal was found to be in a state of negative nitrogen balance, storage of nitrogen beginning with the middle of pregnancy and continuing up to the time of labor, this capacity for storage becoming more marked as the pregnancy advanced, according as the needs of the developing ova became greater.

Jägeroos obtained similar results in his experiments but concluded, after calculating the nitrogen content of the embryos and their appendages, that, taking the time of the pregnancy as a whole, it is to be regarded as a period of sacrifice on the part of the mother.

Ver Eecke, after extensive studies on pregnant rabbits, also concludes that the period of pregnancy is to be regarded as a period of sacrifice by the mother, or, as he expresses it, "a sacrifice on the part of the individual for the sake of the species."

Bar, whose experiments were carried out under more nearly ideal conditions than those of the above-mentioned observers, also recognized two distinct periods in the nutrition of the pregnant animal, corresponding in time to the two halves of the pregnancy; but his findings differ in certain respects from those of Hageman and Jägeroos. In common with them, he

found the second half of the pregnancy to be characterized by a marked and progressive storage of nitrogen up to the time of labor. In the first half of the pregnancy, however, he distinguished two periods; first, a period extending from the beginning of the pregnancy to the second or third week, during which there was a storage of nitrogen, this being followed by what he describes as the period of "saturation," in which the retention of nitrogen is less marked or entirely absent, the animal being either in a state of nitrogen equilibrium or even showing a negative balance. This period continued up to the middle of pregnancy and was believed to be due to an increase in the disassimilation processes. In observations made on two pregnant rabbits he found a storage of nitrogen throughout the whole period of pregnancy. Others were studied, but the results were unsatisfactory.

From the whole series of observations made on pregnant animals, he concluded that in the normal, healthy animal, living under proper hygienic and dietary conditions, and going through a normal pregnancy, the period of gestation is not to be regarded as a period of sacrifice on the part of the mother, but may actually be a period of gain, with an increase in her nitrogen capital.

Murlin, studying pregnant dogs, found a loss of nitrogen throughout the first four weeks of the pregnancy, followed by a marked storage in the second half. One of his animals showed a net gain of 8.69 gm. of nitrogen, while another showed a net loss of 55.6 gm. of nitrogen from the mother's body.

All the observations made on the nitrogen metabolism of pregnant women go to show that, in the second half of the pregnancy, we have a period corresponding to the same period observed in pregnant animals, characterized by the marked ability of the organism to store nitrogen. Beginning with Zacharjewsky, this subject has been more or less extensively studied by Schrader, Sillevs, Slemmons, Hahl and Bar. Slemmons found this capacity for storage to be more marked in multiparæ, whereas Hahl and Bar found it to be greater in primiparous women.

Up to the present time, no one has made any extensive observations on the nitrogen exchange in the early months of a human pregnancy, and it has been more or less assumed that, inasmuch as the needs of the growing ovum are infinitesimal at this stage, there is either no change at all in the general nitrogen metabolism, or that we have a period of loss, as seen in the first half of pregnancy in dogs, and development of the ovum at the expense of the maternal organism.

The earliest extensive observations are those reported by Hoffström, who in a single patient made a very careful study of the nitrogen, sulphur, phosphorus, calcium and magnesium exchange during the last 24 weeks of pregnancy. In this case, personal weekly analyses of the foodstuffs used, and of the urine and feces, were also made.

In regard to the nitrogen metabolism, he found that nitrogen storage occurred throughout the whole period of study. This averaged 1.84 gm. per day, so that the total retention amounted to 310 gm. Of this nitrogen retained, he estimates that 101 gm. were devoted to the development of the ovum, while the balance

of 209 gm. was added to the maternal organism. Of these 209 gm., he estimates that 51 gm. were utilized in the growth and development of the breasts leaving a balance of 158 gm. of "Residual," forming a maternal reserve. He is unable, however, to state the exact form which this reserve takes or the manner in which it is utilized by the organism.

From the study of this patient he draws the following general conclusion: "Normal pregnancy in a healthy maternal organism, living under normal exterior conditions, produces a marked retention of nutritive materials, which suffices for the development of the product of conception and its adnexa, for the modification of the generative organs, and the formation of a reserve fund which will be utilized during labor and the puerperium. Normal pregnancy does not then constitute for the mother a period of loss, nor yet is it for her a period of gain."

During the last two years, we have had the opportunity to make observations on the nitrogen metabolism in three normal pregnancies: in one patient for a period of four weeks, from the tenth to the fourteenth weeks of the pregnancy. The other two patients were studied for the last 133 and 101 days of their respective pregnancies and also for a short time in the puerperal period.

METHOD OF STUDY.

The methods adopted in the study of these patients are quite similar to those used by Slemmons in the cases studied by him in this clinic and reported in 1904. A fairly liberal diet was allowed, both in quantity and character of foodstuffs used. This was particularly true in the first woman, who was a private patient of Dr. Williams, and she was allowed a very wide selection in the choice of her diet. In all instances the patients were allowed sufficient food to satisfy the appetite, but were not compelled to eat all the food allotted for a given meal when they did not desire it. Each article of food was especially prepared for the individual patient, and was carefully weighed or measured before being given to her. The residue, if any, was collected and again weighed or measured. The nitrogen content of the food ingested was computed partly from the tables of Atwater and Bryant and partly from personal analyses. At all times the patients were kept under as normal external conditions as was possible, particularly in regard to exercise, and were not allowed to lead too sedentary a life.

The urine was collected for 24-hour periods, and carefully preserved; of these specimens daily analyses were made. From these daily analyses the daily average nitrogen content of the urine, for periods of a week at a time was estimated. Daily determinations of the ammonia nitrogen were made on all specimens and the amino-acid nitrogen was also estimated for variable periods. The total nitrogen was determined by the Kjeldahl method, the ammonia by the method of Folin and the amino-nitrogen by the Van Slyke method. All determinations were made in duplicate. The feces were preserved and analyzed weekly, and from the results obtained, the average daily nitrogen content was calculated. The patients were weighed at frequent intervals.

STUDY OF CASES.

CASE I.—M. V. W., white, age 28 years. Admitted May 30, 1914. The past history was unimportant.

The present pregnancy is her first, and has been uneventful, except for the fact that the first specimen of urine examined showed the presence of a faint trace of albumin (not in sufficient quantity to give a reading in the Esbach tube). This proved to be a transient phenomenon. Her last menstrual period began on March 7, 1915, and was perfectly normal, lasting for five days. The patient has had no subjective symptoms of any kind since the pregnancy began.

TABLE I, CASE I.
DAILY AVERAGE NITROGEN EXCHANGE.

Week.	Daily N. Intake.	N. Output.			Balance.	Weekly Storage.	Total Storage.	Calories.	Weight, Lbs.
		Urine.	Feces.	Total.					
I.....	13.04	8.10	0.70	8.80	-4.24	29.68	29.68	2499	128½
II.....	10.78	8.06	0.65	8.75	+2.03	14.21	43.89	1973	129½
III.....	10.73	8.22	0.73	8.95	+1.78	12.16	56.35	2081	134½
IV.....	7.88	6.73	0.63	7.36	+0.52	3.64	39.99	1795	130½

The physical examination showed the patient to be a well developed, well nourished woman, in whom no physical abnormalities were detected. The blood pressure was 120 mm. The weight at the beginning of observations was 128½ pounds.

Studies in metabolism were begun on June 2, 1915, and were continued for a period of four weeks. At the time this study was begun, the patient had missed two menstrual periods and was apparently between nine and ten weeks pregnant.

TABLE II, CASE I.

DAILY NITROGEN EXCHANGE. AMMONIA AND AMINO-NITROGEN OF URINE.

Date.	Volume of Urine.	N. Intake.	N. Urine.	N. Feces.	N. Balance.	% of Avg. norm. N.	% of Amino N.	Calories.	Weight, Lbs.
June 2.....	915	12.59	7.30	0.71	+4.58	2.8	3.2	2373	128½
" 3.....	1560	13.30	9.72	0.71	+2.87	3.8	3.2	2578	129½
" 4.....	1090	14.12	4.90	0.71	+8.52	7.1	3.1	2560	130½
" 5.....	1830	12.87	9.48	0.71	+2.67	5.4	3.6	2251	131½
" 6.....	1500	12.86	7.86	0.71	+4.29	3.7	3.8	2572	131½
" 7.....	2120	13.28	9.94	0.71	+2.63	4.4	3.8	2739	132½
" 8.....	1660	12.29	7.55	0.68	+4.06	4.0	3.1	2524	132½
" 9.....	1750	11.89	8.09	0.68	+3.11	3.9	4.3	2150	133½
" 10.....	2030	13.57	9.36	0.68	+3.53	3.9	3.6	2419	133½
" 11.....	1660	12.28	7.74	0.68	+4.16	4.0	...	2293	134½
" 12.....	1390	12.82	7.62	0.68	+4.52	4.7	2.8	2366	134½
" 13.....	1140	3.70	7.74	0.68	-4.71	3.5	...	645	135½
" 14.....	1230	10.17	8.44	0.68	+1.05	4.2	2.1	1832	131½
" 15.....	1460	11.04	7.78	0.75	+2.51	4.7	2.4	2242	132½
" 16.....	1375	10.60	8.00	0.75	+1.85	4.9	3.1	1992	132½
" 17.....	1620	10.99	8.39	0.75	+1.85	8.1	2.4	2106	133½
" 18.....	1910	10.25	7.48	0.75	+2.02	6.0	2.5	2062	134½
" 19.....	1570	11.57	7.94	0.75	+2.19	2.9	3.6	2024	134½
" 20.....	1830	10.01	9.09	0.75	+0.17	3.9	...	2166	133½
" 21.....	1170	11.01	7.78	0.75	+2.48	3.7	2.7	1966	134½
" 22.....	1420	10.39	8.85	0.63	-0.01	6.0	...	1926	134½
" 23.....	1820	9.32	8.85	0.63	-0.16	5.1	2.1	1888	135½
" 24.....	960	7.94	6.59	0.63	+0.72	4.6	3.2	1615	136½
" 25.....	1100	9.30	6.62	0.63	+2.05	8.6	2.4	1875	137½
" 26.....	890	6.89	5.60	0.63	+0.66	4.8	2.6	1549	132½
" 27.....	910	7.43	6.11	0.63	+0.69	5.4	2.0	1629	130½
" 28.....	960	7.43	7.37	0.63	-0.57	4.7	...	1875	130½
" 29.....	830	6.88	5.97	0.65	+0.26	5.7	3.2	1532	130½
" 30.....	750	7.46	4.99	0.65	+1.82	4.7	...	1334	130½

In the study of the daily nitrogen exchange in this patient it was found, as is shown in the tables which follow, that she stored nitrogen from the time of the beginning of the observations and, with the exception of three isolated days, a plus balance was noted on every day during the period of study. On one of the days when a negative balance was noted, the patient had a gastric disturbance, was nauseated and ingested almost no food, the nitrogen balance

on this occasion being -4.71 gm. On the other two occasions, both in the last week of study, the negative balance was very slight, being -.16 and -.57 gm. respectively. On only the one day during the period of study was there any gastric disturbance present, a point which I wish to emphasize.

In Table I, I have tabulated the actual daily average nitrogen exchange for the four weeks during which the study lasted.

Inasmuch as this patient was only observed for a period of four weeks, it seems that it might be advisable to tabulate the actual daily results obtained for comparison with the preceding. Table II shows the actual daily nitrogen exchange during the period of study, together with the ammonia and free amino-nitrogen of the urine for the corresponding days.

CASE II.—J. R., colored, age 19 years. Admitted February 5, 1914.

The past history was unimportant.

The present pregnancy is her first, and has been perfectly normal. The patient has had no nausea or vomiting at any time. Her last menstrual period began on November 15th, and was normal. Fetal movements were first noticed about March 14th.

The physical examination showed no abnormalities.

A study of her metabolism was begun on March 4th, and was continued without interruption throughout the remainder of the pregnancy and for the first week after labor. Her weight at the time the observations were begun was 113 pounds. The following table shows the average daily nitrogen exchange for each week of the study up to the time of labor. (As will be explained later, this patient was delivered about four weeks prematurely, in the 36th week of her pregnancy.) Frequent routine examinations of the urine failed to reveal the presence of albumin, sugar or casts.

TABLE III, CASE II.
DAILY AVERAGE NITROGEN EXCHANGE.

Week of Preg.	N. Intake.	N. Output.			N. Balance.	Weekly Storage.	Total Storage.	Calories.	Weight, Lbs.
		Urine.	Feces.	Total.					
18	10.91	9.46	.54	10.0	+0.91	6.37	6.37	1740	112
19	10.10	6.40	.36	6.76	+3.34	23.38	29.75	1673	112½
20	12.07	8.54	.63	9.17	+2.90	20.30	50.05	1930	113
21	11.80	7.34	.64	7.98	+3.82	26.74	76.79	1930	114
22	11.70	8.88	.67	9.55	+2.15	15.05	91.84	1953	114½
23	12.50	9.61	.55	10.16	+2.34	16.38	108.22	2023	115
24	12.15	9.15	.44	9.59	+2.56	17.92	126.14	1916	116
25	12.30	8.40	.54	8.94	+3.36	23.32	159.66	2012	117½
26	11.87	9.08	.56	9.64	+2.23	15.61	175.27	1906	117½
27	11.72	9.47	.52	9.99	+1.73	12.11	187.38	2133	117½
28	11.76	6.25	.31	6.56	+5.20	36.40	223.78	2042	118½
29	11.56	8.20	.28	8.48	+3.08	20.16	243.94	1974	119½
30	10.40	7.77	.36	8.13	+2.27	15.89	259.83	1722	120½
31	10.90	7.60	.46	8.06	+2.84	19.88	279.71	1672	121
32	11.05	8.30	.40	8.70	+2.35	22.75	302.46	1752	121½
33	12.21	7.77	.52	8.09	+4.12	28.84	331.30	1972	123½
34	11.62	6.69	.57	7.26	+4.36	30.96	362.26	1939	124½
35	11.63	7.49	.40	7.49	+4.14	28.98	391.24	2150	125½
36, 6 days Deliv.	11.80	6.63	.48	7.11	+4.69	28.14	419.38	1683	126½

Labor pains began at 10.00 p. m., July 14th, and after an uneventful labor lasting ten and one-half hours, the child was born at 8.30 a. m., July 15th. (Judging from the menstrual history given by this patient, the time when fetal movements first became evident, and the size of the child, which was somewhat under the average, it seems evident that labor occurred between four and five weeks before full-term, apparently in the 36th week of pregnancy; and I have made calculations on that basis.)

The child weighed 2850 gm. The placenta and membranes weighed 540 gm.; the amount of blood lost was 375 gm. The weight of patient before delivery was 126½ pounds. The weight of patient immediately after delivery was 117 pounds, a net loss of nine and one-half pounds. Observations were continued on the patient for the first ten days of the puerperium and the following results were obtained:

The nitrogen intake averaged 11.34 gm. N. per day.

The nitrogen output:

Urine averaged.....	10.91 gm. per day
Feces averaged.....	.82 gm. "
Lochia averaged.....	.49 gm. "
Milk averaged.....	.70 gm. "

Total output.....12.92 gm. N. per day.

She thus showed a negative nitrogen balance during this period which averaged — 1.58 gm. N. per day. The weight of the patient at the end of the first ten days after labor was 112 pounds, and four days later this had still further decreased to 109 pounds.

CASE III.—E. Z., white, age 18 years. Admitted January 25, 1915. The past history was unimportant.

The present pregnancy is her first and has been normal in every respect up to the time of her admission to the hospital. There has been no nausea, vomiting, or other gastro-intestinal disturbances. Her last menstrual period occurred in the latter part of August, 1914. Fetal movements were first noticed early in January, 1915.

The general physical examination showed a healthy woman in whom no abnormalities could be detected. The fundus of the uterus was two fingerbreadths below the level of the umbilicus. Active fetal movements were readily appreciated, and the fetal heart-sounds distinctly heard.

Observations on this patient were begun on January 27th and were continued without interruption throughout the remainder of pregnancy and for the first week of the puerperium. Her weight at the time the study was begun was 115 pounds. Frequent routine examinations of the urine throughout the period of study failed to show the presence of sugar, albumin or casts at any time.

From the history of the patient, and the findings at examination, it seems fair to conclude that this woman was apparently in about the 23d or 24th week of her pregnancy and was delivered about two weeks before the expected date of confinement, in the 38th week of the pregnancy.

In the following table is tabulated the average daily nitrogen exchange, together with the average and total storage according to the same scheme as that employed in the preceding case.

TABLE IV, CASE III.
DAILY AVERAGE NITROGEN EXCHANGE.

Week of Preg.	N. Intake	Urine	Feces	Total	N. Balance	Weekly Storage	Total Storage	Calories	Weight Lbs.
24	15.33	11.31	0.86	12.17	+3.16	22.12	22.12	2310	116½
25	15.65	12.90	1.17	14.07	+1.75	11.64	33.76	2321	115½
26	15.98	11.66	0.80	12.46	+3.52	24.50	58.26	2418	120½
27	15.83	13.13	1.60	14.73	+1.10	11.48	69.74	2506	119½
28	15.94	12.41	1.34	13.75	-1.79	12.78	82.52	2588	121½
29	15.87	13.70	1.71	15.41	+0.49	3.22	85.74	2665	122½
30	16.28	13.39	1.39	14.78	+1.50	15.77	101.51	2416	122½
31	16.39	13.77	1.40	15.17	+1.22	11.06	112.57	2448	125½
32	16.99	14.27	1.27	15.54	+1.45	10.64	123.21	2532	125½
33	15.50	14.06	0.88	14.94	-0.56	24.95	148.16	2765	127½
34	19.72	15.78	0.66	16.44	+3.28	43.96	192.12	2588	129½
35	20.57	15.58	0.81	16.39	+4.18	43.19	235.31	2945	129½
36	19.62	15.08	1.17	16.25	+3.37	44.59	279.90	2777	131½
37	19.52	12.42	1.11	13.53	-6.04	42.28	322.18	2681	134½
38 4 days	19.84	15.77	1.35	17.12	-6.72	29.16	351.34	2687	134½
Deliv.	7.76	21.11	1.65	22.76	-15.00				

Labor pains began at 1.00 a. m., on May 8, 1915, the entire labor being uneventful and ending spontaneously after a duration of 15 hours.

The child weighed 2960 gm. The placenta and membranes 480 gm. The amount of blood lost was 150 gm. The weight of patient before delivery was 133½ pounds. The weight of patient

immediately after delivery was 121¼ pounds, a net loss of 12 pounds.

The puerperium was perfectly normal, and the nitrogen exchange during the first week after labor was found to be as follows:

The nitrogen intake averaged 18.03 gm. N. per day.

The nitrogen output:

The urine averaged.....	15.96 gm. N. per day
The feces averaged.....	1.06 " "
The lochia averaged.....	3.40 " "
The milk averaged.....	0.32 gm. "

Total output.....20.74 gm. N. per day.

Thus, there was a negative nitrogen balance, which averaged — 2.71 gm. of nitrogen per day.

The weight of the patient at the end of the first week after labor was 117¼ pounds, and on May 23d, fifteen days after delivery, this had decreased still further to 115 pounds.

DISCUSSION OF RESULTS.

In considering these observations, one point to be emphasized is the fact that all three were made upon perfectly healthy women presenting perfectly normal pregnancies, and that none of them suffered from nausea, vomiting, or any of the other gastro-intestinal disturbances so frequently noted in early pregnancy. Indeed, inasmuch as it has been our experience that at least half of our patients go through the entire period of pregnancy without any of these disagreeable symptoms, the question arises as to whether the women suffering from such disturbances are to be regarded as being perfectly normal.

Case I, so far as I am aware, is the earliest pregnancy on which metabolism studies have been carried out for any extended period of time. In this patient storage of nitrogen was found to be taking place from the time the observations were begun until their close, and in the actual daily exchange a positive balance was noted on every day except three. The total storage of nitrogen during the period of observation amounted to 59.99 gm. N.

The period of observation in this patient probably extended from the tenth to the fourteenth weeks of her pregnancy at the latest, and it may have been begun slightly earlier. At this period of pregnancy the daily need of the developing ovum for nitrogen can be regarded as infinitesimal. Indeed, the total nitrogen content of the entire ovum probably does not exceed two or three grams, whence we may conclude that most of the nitrogen stored must have been added to the general maternal organism in some form, possibly to be drawn on later by the developing ovum when its needs became greater. In regard to the place of storage and the form assumed by this nitrogen, it is of course quite impossible to make any positive statement; although we must bear in mind that even at this early stage a portion of it is probably utilized in the growth and hypertrophy of the uterus and breasts.

Storage was found to be most active during the first three weeks of the study and was accompanied by an increase in the body weight of 1½ pounds. In the fourth week the conditions were quite changed, inasmuch as the average daily intake now fell to 7.88 gm. N. per day, and with this marked diminu-

tion in the intake (the caloric value of the diet at this time was not sufficient for a patient of her body weight) the patient lost four pounds in weight, as compared with the weight at the end of the preceding week. How is this to be explained?

One explanation might be in the possibility that she may have reached what Bar describes as the "period of saturation," in which disassimilation processes predominate. It is to be noted, however, that this marked change was not accompanied by any gastro-intestinal disturbances. Consequently, I am inclined to believe that the true explanation is much simpler, and that the change was due entirely to the fact that the patient had become thoroughly tired of the diet and régime to which she was being subjected and was suffering from anorexia. The weather, too, at this time had become very oppressive. Confirmation is lent to this belief in the fact that as soon as the patient left the hospital, and lived under home surroundings, her appetite returned and she again began to take her food with relish and increased rapidly in weight.

One very striking feature during the last week of this observation is the fact that in spite of the very low nitrogen intake, as well as the fact that she was losing in weight, she still had the capacity for storing nitrogen, though to a much less degree than during the three preceding weeks.

The second case in our series about corresponds, so far as the period of the pregnancy is concerned, to the case studied by Hoffström. Our patient went into labor, however, about a month before the expected date of confinement, so that observations were carried out only for the last 19 weeks of her pregnancy. That she was delivered about four weeks prematurely is, I think, evident when we consider her menstrual history, the time when the foetal movements first became perceptible, as well as the fact that the child was somewhat under the average weight.

As is shown in the accompanying table (Table III), in which I have set down the daily average exchange, this patient was also found to be storing nitrogen from the time observations were begun. As in the preceding case, a chart of the actual daily nitrogen exchange was also kept, which shows that on occasional days, as in Case I, there was a slight negative nitrogen balance.

In studying these patients it was thought that possibly cyclical variations in the nitrogen exchange might be noted at periods of time corresponding to the time of the menstrual periods, had the patient not been pregnant, but such was not found to be the case.

Although this patient was at all times allowed sufficient food to satisfy her appetite, nevertheless, her daily intake throughout the entire period was strikingly low, at no time being greater than 12.5 gm. N. per day. Storage became particularly active from the nineteenth to the twenty-first weeks, at the time when foetal movements were becoming particularly active.

The low nitrogen content of the feces is probably to be accounted for partly by the low nitrogen intake and partly by the easily digestible diet of the patient.

As in Hoffström's case, the most active storage took place during the last nine weeks of the pregnancy when the foetal

needs were at a maximum. The total nitrogen stored by this patient during the period of observation, amounted to 419.38 gm. N. It is interesting to try to determine what became of this nitrogenous material, although this, of course, can only be determined approximately.

The child weighed 2850 gm. Michel, in his analyses of human foetuses, found the nitrogen content of a child weighing 3335 gm. to be 12.1 gm. N. Calculating on this basis, which in this case, however, can only be approximate, the nitrogen content of the child alone ought to be 62.1 gm.

The placenta was not analyzed. Its weight, without cord and membranes, was 500 gm. As shown by Koelker and Slemmons, one-half of the fresh weight is made up of foetal blood, whereas the weight of the dried, water-free material amounts to 7 per cent of the fresh weight of the organ, and the nitrogen content of this dried material to 14.9 per cent. Making use of these findings, we calculate that the nitrogen content of the placental tissue would be 5.21 gm. N., and upon adding to this the nitrogen content of the foetal blood, which should amount to 9.45 gm., we estimate that the total nitrogen content of the organ is approximately 14.66 gm. We may allow 2 gm. (an extreme figure) as the nitrogen content of the cord and membranes, which weighed 40 gm.

Deducting the weight of the child, placenta and membranes, and blood lost at the time of delivery, from the total loss of weight of the patient at the time of labor, we find the amount of amniotic fluid to be approximately 540 gm. which, from the figures given by Hoffström, would contain 0.19 gm. N.

The nitrogen content of the ovum, then, may be tabulated as follows:

Child	62.10 gm. N.
Placenta	14.66 "
Cord and membranes.....	2.00 "
Amniotic fluid.....	0.19 gm.

Total nitrogen content of ovum	78.95 gm. N.
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Hoffström estimates the nitrogen content of the entire ovum at the end of the seventeenth week of pregnancy to be 5.11 gm. Accepting this figure as being correct, we find then that, of the 419.38 gm. N. stored by this patient, 73.54 gm. have been diverted to the growth and development of the ovum. This leaves a balance of 345.84 gm. N. which have been added to the general maternal organism. From this amount, however, we ought to deduct the nitrogen content of the blood lost at the time of labor, and which amounted to 5.56 gm., leaving a balance of maternal storage of 340.28 gm.

A certain proportion of this has, of course, been utilized in the hypertrophy and development of the genital organs incident to the pregnancy, more particularly the uterus and breasts.

The uterus increases in size up to 800 or 1000 gm. Slemmons found the nitrogen content of a uterus removed by supravaginal amputation following Cæsarean section, and weighing 850 gm. in the fresh state, to be 38.75 gm.

Assuming the hypertrophy of the breasts to amount to half a kilogram, this would account for approximately another 11 gm. N. We thus have approximately 55.75 gm. of the

maternal storage diverted to the development of the genital organs, but we still have left a balance of 284.53 gm. N. added to the maternal organism, which Hoffström describes as "Rest-material."

In the third patient, observations were begun at a rather later period, at approximately the twenty-fourth week of the pregnancy.

One very noticeable feature in this patient is the fact that her nitrogen intake was always greater than in the preceding case, at times almost double; and another very striking feature is the marked increase in the N. intake during the last five and a half weeks of the pregnancy. This was entirely voluntary on the part of the patient, and the diet was simply increased to the point of satisfying her appetite, no artificial element in the way of forced feeding being introduced. Her body-weight increased 16 $\frac{3}{4}$ pounds during the time of observation, as compared with 14 $\frac{1}{2}$ pounds in Case II, during a somewhat longer period.

As in Case II, this patient was found to be storing nitrogen to a marked degree from the beginning of the observations (see Table IV), although she also showed an occasional slight negative balance in the actual daily exchange. The most active storage occurred during the last five and a half weeks of the pregnancy as compared with the last nine weeks in the preceding case, and this also corresponded to the time when the diet was at its maximum.

The total storage of nitrogen during the 14 $\frac{1}{2}$ weeks the patient was under observation amounted to 336.21 gm.

Using the same basis for the calculations as in the preceding case, I have estimated below the amount of the stored nitrogen which has been diverted to the development of the ovum:

	Weight.	Nitrogen Content.
Child	2960 gm.	64.5 gm.
Placenta	420 "	11.73 "
Membranes and cord....	60 "	2.0 "
Amniotic fluid.....	1845 "	0.68 "
Total		78.91 gm.

Hoffström estimates that the nitrogen content of the entire ovum at the end of the twenty-third week amounts to 14.26 gm. Of the 336.21 gm. of nitrogen stored, therefore, we then find that 64.65 gm. have been diverted to the growth and development of the ovum. In this patient, then, we have had 271.56 gm. N. added to the general maternal organism. Again deducting the nitrogen content of the blood lost at the time of delivery, and which amounted to 4.83 gm., we have a maternal balance of 266.73 gm. N.

If, as in the previous case, we allow 38.75 gm. N. for the development of the uterus, and 17 gm. N. for the breasts, we still have a maternal balance of 210.98 gm. N. as "Rest-material."

In these two cases, the amounts of nitrogen allowed for the development of the genitalia, and the estimated nitrogen content of the ovum are, of course, only approximate. However, I think they are sufficiently accurate to show us that, in normal

human pregnancy, the storage of nitrogen by the maternal organism is far in excess of the actual needs of the developing ovum, and indeed may be several times the amount actually needed for its development.

As to the form in which the "Restmaterial" is stored, definite statements cannot be made as yet. A certain portion of it is doubtless made use of in the formation of new blood. As shown by Miller, Keith and Rowntree, the blood volume is very definitely increased at the end of pregnancy. Indeed, in Case III of this series the woman was one of the subjects of their observations, and at a time four weeks before her delivery the blood volume was estimated to be 5408 cc. This, however, would only account for a small portion of the "Restmaterial." A portion also is probably utilized in the hypertrophy of muscles and the various glandular structures affected by pregnancy. In regard to the remainder, Hoffström accepts the hypothesis that this is stored as unorganized protein, as a reserve material; and for the present, until definite proof in regard to its disposal can be adduced, this seems to offer a very plausible explanation.

This reserve is probably drawn upon extensively during the puerperium and period of lactation, during which the entire reserve supply is possibly exhausted.

Cases II and III of our series were both studied for periods of ten and seven days respectively after labor. Unfortunately the observations could not be carried on longer. The results obtained did not differ from those of Slemmons and other observers. Both patients showed a negative nitrogen balance, decreased in weight, and both were losing nitrogen when the observations were brought to a close.

AMMONIA AND AMINO-ACID NITROGEN.

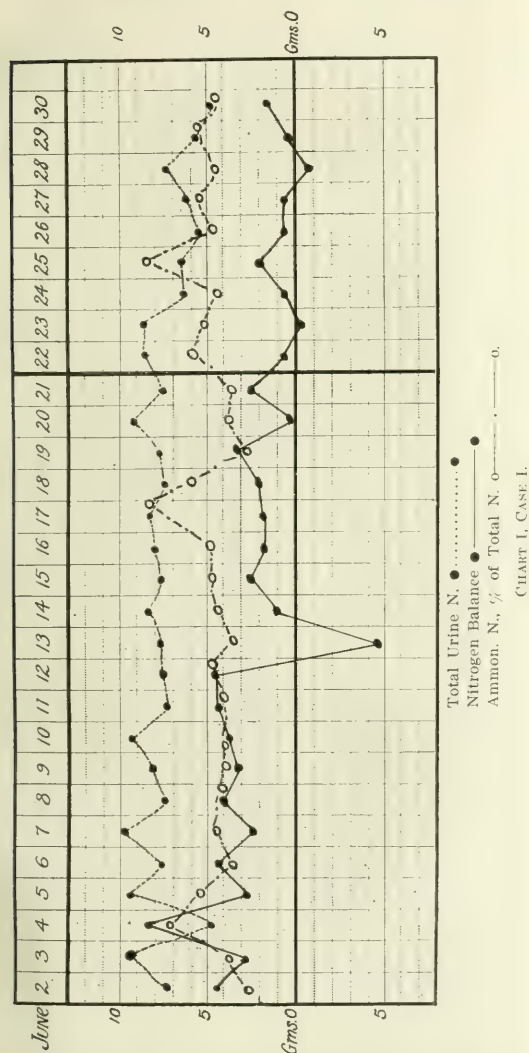
In Case I, daily estimations of the ammonia nitrogen present in the urine were made by Folin's method, and its percentage was found to be practically normal; although on one occasion it made up 8.6 per cent of the total urinary nitrogen. The extremes were 2.8 per cent and 8.6 per cent, with an average for the time of observation of 4.8 per cent of the total nitrogen. The daily figures are shown in Table II (see also Chart I).

This is a somewhat lower average percentage of ammonia nitrogen than is generally present in the urine during late pregnancy, as Slemmons and Murlin both found rather higher figures.

In this patient the free amino-nitrogen was also determined by the method of Van Slyke, on every daily total specimen of urine, except on five occasions. These daily percentages of amino-nitrogen are also shown in Table II, and are seen to be somewhat higher than those generally given for the non-pregnant individual (stated by Van Slyke to be about 1 to 1 $\frac{1}{2}$ per cent of the total nitrogen). The extreme figures found were 2.0 per cent and 4.3 per cent of the total nitrogen, with an average of 2.97 per cent for the whole period of study. Landsberg, in his series of observations on ten pregnant women, found an average of 3.8 per cent of amino-nitrogen in the urine during the latter part of pregnancy, as compared with 2.8 per cent

in a series of non-pregnant individuals, his estimations being made by the formol-titration method. Falk and Hesky and Frey also found an apparent increase in the amino-nitrogen.

In Case II, daily estimations of the ammonia nitrogen were also made throughout the entire period during which the



patient was under observation. In the earlier weeks, the results obtained about correspond to those in Case I and are well within normal limits. During the last six weeks of the pregnancy, however, there was a slight, but still a very definite, increase in the percentage of ammonia nitrogen, although this

never reached what would be regarded as an abnormal figure. On the day on which labor began, July 14, there was a very pronounced increase in the percentage of ammonia nitrogen, which reached 19.8 per cent of the total urinary nitrogen.

The free amino-nitrogen of the urine was determined daily for a period of five weeks from the thirty-first to the thirty-fifth weeks inclusive. The highest figure obtained on any one day was 5 per cent and the lowest 1 per cent of the total urinary nitrogen, while the average daily percentage for the whole period was 2.56 per cent, which practically corresponds to the results obtained in Case I in the early weeks of pregnancy. The daily average ammonia nitrogen and amino-nitrogen percentages for each week are shown in Table V, and the daily percentage of ammonia nitrogen for the last 10 days of pregnancy and day of delivery are given in Chart II.

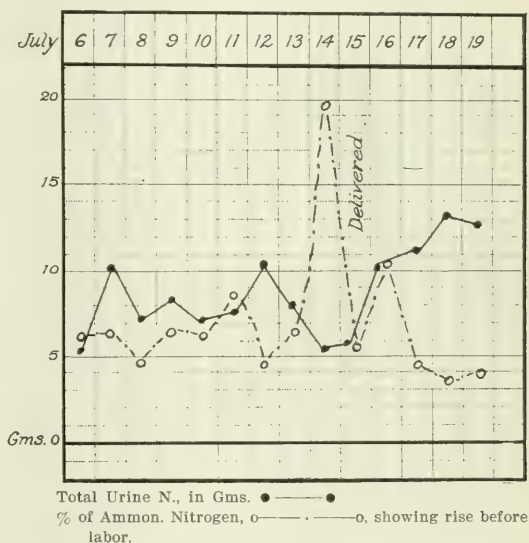


CHART II, CASE II.

Daily estimations of the ammonia nitrogen in Case III also showed the percentage to be well within normal limits throughout the entire period. In this patient there was no decided increase during the last weeks of the pregnancy, as was noted in Case II, the ammonia percentage remaining remarkably constant throughout the entire period. The absence of such a rise in the ammonia percentage in this case is probably to be explained by certain differences in the diet of the two individuals, Case III ingesting and eliminating much larger amounts of nitrogen than did Case II; consequently, slight variations in the actual daily amount of ammonia eliminated would produce little or no change in the percentage of ammonia nitrogen. There was a decided rise, however, in the percentage of ammonia nitrogen on the day of delivery, reaching 8.6 per cent of the total nitrogen. The daily percentages of ammonia nitrogen for the last 10 days of pregnancy and

the day of delivery are shown in Chart III. The fact that the rise in percentage of ammonia nitrogen was found on the day of delivery in Case III, and on the day preceding delivery in Case II, is to be explained, I think, by the fact that in Case III

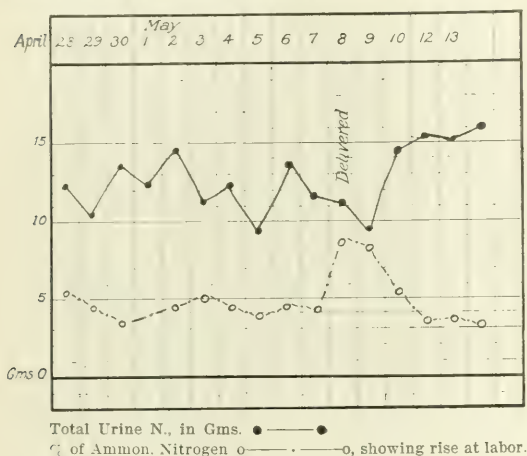


CHART III, CASE III.

labor began shortly after the termination of a 24-hour period of observation, whereas in Case II labor had already been in progress for some hours before the 24-hour period had been completed, and in our studies it was not feasible to make analyses of the excreta at shorter intervals than 24 hours. In the cases

TABLE V, CASES II AND III.

DAILY AVERAGE PERCENTAGES OF AMMONIA NITROGEN AND AMINO-NITROGEN.

Case II.			Case III.		
Week.	Per cent of Ammonia N.	Per cent of Amino-N.	Week.	Per cent of Ammonia N.	Per cent of Amino-N.
18	5.66
19	4.80
20	4.70
21	1.64
22	4.64
23	3.70
24	3.98	...	24	5.50	1.82
25	5.22	...	25	4.97	1.75
26	5.22	...	26	4.45	2.24
27	4.70	...	27	4.35	...
28	5.32	...	28	3.94	...
29	4.76	...	29	3.87	...
30	5.80	...	30	3.99	...
31	6.45	3.14	31	3.99	...
32	5.57	2.48	32	3.66	...
33	6.31	1.98	33	3.66	...
34	6.85	2.07	34	4.00	...
35	6.20	3.13	35	4.24	...
36	8.76	...	36	4.60	...
37	37	4.50	...
38	38	4.10	...

studied by Slemmons the highest percentages of ammonia nitrogen were found on the day of delivery, but in three of his cases there was also a very definite increase on the day preceding the onset of labor.

For the first three weeks this patient was under observation, daily estimations of the free amino-nitrogen were also made.

Somewhat lower figures were obtained than in Cases I and II during the earlier and later weeks of pregnancy and a slighter degree of variation in the daily figures was noted. The extremes were 1.1 per cent and 3.2 per cent of the total urinary nitrogen, and the daily average for the three weeks was 1.97 per cent. The daily average percentages of ammonia and amino-nitrogen for the period during which observations were made are shown in Table V, together with the same figures for Case II.

From the observations made on the amino-nitrogen of the urine in our three patients at various periods of pregnancy, it would seem that there is a definite increase in the percentage of nitrogen eliminated in this form. This increase, however, is largely a relative one, the percentages being higher on account of the decrease in the total nitrogen of the urine.

CONCLUSIONS.

1. In the perfectly normal pregnant woman, storage of nitrogen begins at a much earlier period than has hitherto been supposed; possibly the organism may acquire the capacity for storing nitrogen from the very beginning of the pregnancy.

2. In the early months this storage is far in excess of the actual needs of the developing ovum, and the excess must be added to the general maternal organism.

3. Storage of nitrogen continues throughout the entire duration of pregnancy, being most marked during the last few weeks, when the fetal needs are at a maximum.

4. The nitrogen stored is greatly in excess of the actual needs of the developing ovum, so that, apart from the amount needed for the hypertrophy and development of the genitalia and breasts, a large proportion of the nitrogen stored is added to the general maternal organism as "Restmaterial," though, concerning the form in which this reserve is stored, we are unable to make any positive statement. The nitrogen capital of the maternal organism is thus increased, though the reserve supply may possibly be entirely exhausted during the puerperium and period of lactation.

5. In the healthy woman, who goes through a normal pregnancy, the period of gestation does not necessarily represent a "sacrifice of the individual for the sake of the species," but may actually be a period of gain.

6. There is a relative increase in the percentage of urinary nitrogen excreted in the form of free amino-acids, though not necessarily an absolute increase in this form of nitrogen.

7. There is also a tendency for the percentage of ammonia nitrogen to become increased during the last weeks of pregnancy, although at other times during the pregnancy there is practically no variation from the percentages noted in non-pregnant individuals upon a similar diet.

In conclusion I wish to express my gratitude to Prof. J. Whitridge Williams for the privilege of carrying out this work; also to the various members of the resident obstetrical staff for much valuable assistance in supervising the régime under which these patients were kept.

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FUNCTIONAL SIGNIFICANCE OF MITOCHONDRIA IN TOXIC THYROID ADENOMATA.

PRELIMINARY REPORT.

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It has been customary in the past to group under the designation "thyroid adenomata" new growths of benign nature occurring in the thyroid gland in the form of rather well-defined nodules or even encapsulated tumors that are usually readily distinguishable from the adjoining normal thyroid parenchyma. These adenomata are further subdivided upon the basis of their histological structure into colloid, cystic and foetal adenomata. Whether the latter are or are not suitable classifications I shall not discuss at the present time. The terms colloid and cystic are self-evident as applied to their structure, while in the case of those adenomata whose structure is exceedingly variable, and in which atrophic-looking, colloid parenchyma alternates with hyperplastic-looking parenchyma quite different from the ordinary thyroid structure, the term "foetal adenoma" has been applied upon the assumption that these tumors had their origin in embryonic remnants.

The histological structure of these adenomata suggests in the majority of instances relative functional inactivity; that is, if the assumption of functional inactivity as compared with overactivity is based upon the histological criteria ordinarily applied to the study of the thyroid gland. The criteria of overactivity, namely, the increased height and size of the thy-

roid cells, the infolding and general hypertrophy and hyperplasia of the thyroid parenchyma and the diminished size of the acini containing little or no colloid, when applied to these adenomata, would lead one almost surely to the conclusion that in the absence of these criteria the tumor in question is an inactive one. Now it is just in these circumscribed tumors that one so frequently finds the parenchyma consisting in the main of low cuboidal or even flattened epithelium, with small, often pycnotic nuclei, a considerable, often very abundant amount of colloid, absence of infolding of the follicular epithelium and of evidence of hypertrophy and hyperplasia generally of the thyroid epithelium. In spite of these facts one frequently encounters clinical states of undoubted hyperthyroidism associated with the occurrence in the thyroid gland of such circumscribed nodules. The hyperthyroidism symptoms may be very mild and hardly perceptible, or in some instances they may be extreme. In certain cases, however, the thyroid lesion may be present without any discoverable symptoms pointing to a condition of hyperthyroidism. To explain these symptoms of thyroid overactivity many have assumed that as a result of the mechanical pressure exerted upon the adjoining normal thyroid gland, the secretion of the

latter has been squeezed in excessive amounts into the circulating fluids and has thus caused the symptoms of hyperthyroidism. Another explanation offered is that the mere presence of the tumor acts as a mechanical irritant to the gland, thus exciting the latter to overactivity. By others the symptoms of hyperthyroidism have not been explained at all, the statement simply being made that their origin must be looked for elsewhere than in disorders of the thyroid gland. And lastly, in some instances the adenoma was held responsible, despite the fact that no satisfactory histological evidence of its hyperactivity was apparent.

Patients with evidently inactive adenomata present themselves to the surgeon principally for the removal of the growth for cosmetic reasons or for the relief of mechanical pressure upon the trachea and oesophagus. It is a common experience in the other cases, those presenting symptoms of hyperthyroidism, that, after the surgical removal of the adenoma, such symptoms rapidly subside. This experience lends support to the assumption that the tumor itself is responsible for the symptoms of thyroid overactivity.

An example of this kind may be given, illustrative of conditions in other patients who have recently come for treatment to the surgical clinic of Professor Halsted. A thyroid tumor had existed for a number of years, at first unassociated with symptoms suggestive of hyperthyroidism, presenting, however, in the last year and a half definite symptoms of moderate thyroid intoxication. At operation upon the thyroid an encapsulated tumor was removed and upon histological examination was found to have the appearance of a simple inactive colloid adenoma (*cf.* photograph, Fig. 2). Furthermore, upon physical examination of the patient before operation, the thyroid gland itself did not present any findings suggestive of overactivity, such as increased vascularity; nor did the gland at operation suggest such a condition. Following the operation, however, there was a marked improvement in the patient's general condition. This fact goes to indicate that the adenoma must in large measure have been responsible for the production of the symptoms of hyperthyroidism.

The first patient illustrating these points, whom I had the privilege of observing, was one who came to the surgical clinic of the Peter Bent Brigham Hospital, Boston, Mass., March 11, 1914. It is for this reason and because of the fact that this case illustrates the findings in several recent cases admitted to the surgical clinic of The Johns Hopkins Hospital that I shall briefly review the history and examination.

The case was that of a married woman, aged 37 years, who complained of a lump in her neck (*cf.* Fig. 1), recent difficulty in swallowing, and nervousness. She was admitted to the surgical clinic of the Peter Bent Brigham Hospital, March 11, 1914.

The family history is unimportant. There has been no similar trouble in any of her ancestors.

Past History.—She had scarlet fever at the age of five years, but no other acute illness. She has occasionally suffered with headaches, sore throat and tonsillitis. She has had some dyspnea. The digestion has always been good; the bowels have been constipated. The genito-urinary and menstrual histories are negative. She has had four children, living and well. Her husband was accidentally killed while at his work one and a half years before

her admission to the hospital. She attributes the onset of her nervous symptoms to this cause. Her habits are good. *Weight*, March 18, 58.8 K. (129.3 pounds).

The *present illness* dates back five or six years, to a time just after the birth of her last child. She noticed that the neck was getting larger owing to the appearance of a lump in the lateral margin of the right thyroid lobe. The lump was very small at this time, perhaps the size of a marble. Two or three years ago there was a slight enlargement, and in the past four to five weeks the nodule has been growing more in the direction of the isthmus. The lump has never been painful and has never caused the patient any noticeable trouble until in the past four to five weeks, when there has been slight difficulty in swallowing. Slight hoarseness of the voice has also been noticed recently. *Slight palpitation* has been apparent for four or five years and has grown distinctly worse since the death of her husband a year and a half ago.

Symptoms of nervousness and worry have been present for the past two years, but have gotten distinctly worse following an attack of tonsillitis four weeks ago.

Increased perspiration, hot and cold flushes, salivation and some loss of weight, have also been noticed during the past four weeks. *Asthenia and loss of appetite* have been rather marked recently. *Constipation* has been troublesome for several years.

Physical Examination.—The positive findings, many of which point to a mild degree of hyperthyroidism, may be summarized as follows: The patient is a poorly nourished, restless, rather nervous, middle-aged woman.

There is increased perspiration of the palms of the hands, axillae and soles of the feet.

Eyes.—The Möbius and Dalrymple signs are positive. There is a slight widening of the lid-slits, but no exophthalmos and no von Graefe's sign are apparent. The hair has tended to come out in increased amounts recently. There is some increased pigmentation of the skin.

Neck.—In the region of the right lobe and right half of the isthmus of the thyroid gland is an irregular prominent swelling, about the size of an egg. There is no enlargement of the left lobe. There is no venous distention of the superficial vessels to be noted and no apparent increase in the carotid pulsation or in the pulsation of the thyroid gland itself.

Measurements of the Neck.—

Circumference at level of thyroid cartilage.....	.32 cm.
Circumference over middle of isthmus.....	.35 cm.
Circumference at root of neck.....	36.5 cm.

Measurements of Nodule in Right Lobe and Isthmus.—

Transverse diameter.....	7.5 cm.
Vertical diameter.....	4.5 cm.

Palpation.—There are no thrills palpable over the poles of the thyroid gland or over the tumor itself. The tumor is circumscribed; it can be readily displaced upward into the neck and apparently arises from the right thyroid lobe. It is elastic to the feel, not fluctuant, and has the consistency of a colloid nodule. The left lobe of the thyroid gland is not distinctly palpable. The right lobe, aside from the nodule, is not distinctly palpable.

Auscultation.—No bruits are heard over the poles of the thyroid gland or over the tumor.

Teeth.—The few that remain are in bad condition. Most of the teeth have been extracted.

Chest.—No retrosternal dullness. Heart and lungs negative.

Mammary glands atrophic. Montgomery's glands hypertrophic.

Abdomen.—Edges of liver and spleen just felt. No epigastric pulsation. Adipose tissue lacking in the skin.

Extremities.—Perspiration of hands and feet noticeable. They are quite cold. No edema of legs.

Reflexes.—Superficial reflexes inactive. Deep reflexes active.

Tremor not characteristic. A slight unsteadiness in the hands is perceptible. The patient has been resting in bed for six weeks.



FIG. 1.—Photographs of the patient, showing the circumscribed tumor of the right lobe and isthmus of thyroid gland. Note the absence of exophthalmos.

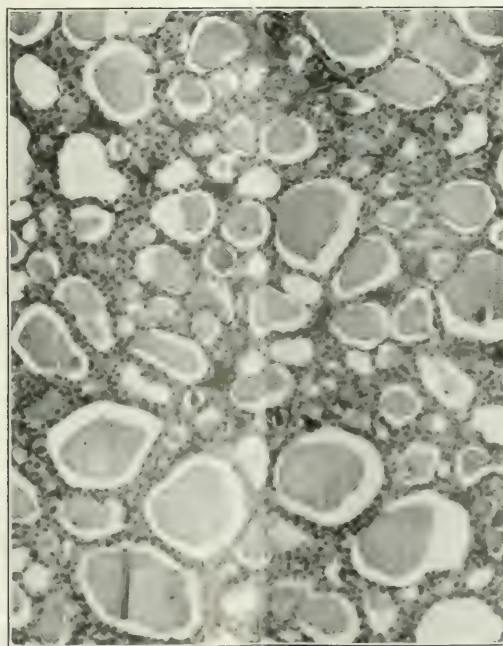


FIG. 2.—Photomicrograph (chromesublimite fixation and hematoxylin-eosin stain; 4 mm. in thickness) of a section representative of the general appearance of the adenoma in the thyroid gland. Note the relatively large amounts of intrafollicular colloid and the absence of the common evidences of hyperthyroidism and hyperplasia of the thyroid epithelium. ($\times 100$.)

Temperature varies between 97° and 98°.

Pulse averages about 70 per minute.

Urine negative. Output varies between 1300 and 1500 cc. in 24 hours.

Blood Examination.—W. B. C., 12,400; hæmoglobin, 78 per cent. The differential count shows no abnormal findings.

Blood Pressure.—Systolic, 120 mm. Hg.; diastolic, 74 mm. Hg.

Pharmacodynamic Tests.—The patient gives a practically negative response to the hypodermic injection of 0.00075 gm. of atropin. There was a marked response to the hypodermic injection of 0.0075 gm. of pilocarpine, especially evidenced by the profuse perspiration, salivation and coldness of the extremities produced. The pulse rate was somewhat diminished, but no change in the respirations or temperature was observed.

The tolerance to levulose by mouth is approximately 150 gms. Glucose 100 gms., when given by mouth and followed by the hypodermic administration of adrenalin 0.00075 gm., does not produce a glycosuria.

Operation.—March 21, 1914. *Excision of encapsulated fatal adenoma in the right thyroid lobe and isthmus.*

The tumor was found to possess a definite capsule. It was inclosed within the normal-appearing right thyroid lobe, which was considerably thinned out over the tumor. The latter shelled out readily and was about the size of a small lemon. The left thyroid lobe was explored and gave all the appearances of being normal. There were no evidences of hypertrophy or hyperplasia of the thyroid gland, which also failed to show any evidence of increased vascularity.

Gross Pathological Examination.—The tumor is about the size of a small lemon. It possesses a distinct capsule and weighs 33 gms. Attached to it is a section of normal-appearing thyroid tissue. At the right border of the nodule is a separate distinct enlargement, the size of a cherry.

On cross-section the tumor is seen to be composed of a soft pulpy tissue, dark red in color; and interspersed in it are seen irregular islands of whitish, apparently hyperplastic tissue. In one area there is a small cyst, containing a thin straw-colored fluid and lined with a soft reddish granular tissue. In the wall of the cyst is a plaque of calcification. Other granules of calcification are seen scattered through the tumor. In certain areas the parenchyma contains a considerable amount of colloid. Nowhere is there apparent any normal-appearing thyroid gland. The smaller nodule on the right border of the tumor on cross-section is seen to consist of a pale yellowish parenchyma containing small whitish islands of tissue and a moderate amount of colloid.

Microscopic.—Fig. 2 ($\times 100$) represents a photomicrograph of an area typical of the greater portion, in fact, of almost the entire adenoma. In certain areas there are aggregations of small follicles, many of which lie free in a matrix of interacinar colloid. The latter does not seem to have resulted from traumatic rupture of intact follicles, for the follicles, in the areas in question, are not broken and there is no evidence of hemorrhage. The follicles vary in size, nowhere being extremely large. There are many small ones. Intrafollicular colloid is present in fairly abundant amount. The follicular epithelium is everywhere of the low-cuboidal and even in many cases of the flattened type, and nowhere is papillary infolding of the epithelium apparent. There are no signs of the characteristic hypertrophy and hyperplasia of the thyroid epithelium. Nowhere does one see tall, columnar epithelium. In certain areas between the larger follicles there are aggregations of smaller follicles, apparently newly formed. The cytoplasm of the cells on the whole is moderately abundant. It stains well with eosin, and in it, upon close observation, is seen a sprinkling of fine pink-staining granulations. (The latter upon subsequent study proved to be mitochondria.) The nuclei stain well in hæmatoxylin. They are vesicular, oval or flattened, and contain usually a well-marked centrosome and numerous dark-staining chromatin granules. The oval or flattened nuclei are

most often pycnotic. There is no apparent increase in vascularity. Basing one's opinion upon these histological facts, one would conclude that the adenoma is functionally inactive.

Pathological Diagnosis.—"Fetal adenoma" of the thyroid gland.

Upon examination 11 days after operation, except for some feeling of weakness and loss of appetite, the patient's general condition was considerably improved. There was definite improvement in her previous symptoms of nervousness, palpitation, worry, "hot and cold flushes," and increased perspiration. The pulse rate, which before operation was relatively slow, showed a slight fall, being occasionally as low as 65 per minute.

The temperature varied between 97.4° and 98.6°. The respirations were 20.

The skin was drier than before operation.

All the eye signs of exophthalmic goitre were negative, including the Möbius sign, which was positive before the operation. There was no unsteadiness of the eyeballs in the extreme lateral position.

There was no difficulty in swallowing.

The neck, except for the results of the extirpation of the gland, was as before operation.

Reflexes as before.

Tremor, none.

There had been a loss in weight of 1.3 K. (2.86 pounds) since the operation.

The responses to the hypodermic administration of atropin and pilocarpin in the same dosage as before operation were definitely less.

One year following operation patient reports that she weighs 142 pounds (a gain of 12.7 pounds), and that she has been definitely benefited by the operation. Her pulse rate is 62 per minute. There is no tremor. Slight nervousness and palpitation persist. She reports also that she is taking care of a large family, a fact to which she attributes several of the symptoms which still persist but to a milder degree than before.

To summarize, then, we have here an illustrative case of a woman of middle age who showed in the thyroid gland a circumscribed swelling which had been present for several years, apparently unassociated with any recognizable symptoms. In the last year and a half a number of symptoms of mild hyperthyroidism had supervened along with the history of more rapid enlargement of the nodule. Before and at operation the thyroid gland itself did not suggest the appearance of overactivity. After removal of the tumor, considerable benefit to the patient ensued not only from relief of mechanical pressure, but also in regard to the symptoms of hyperthyroidism. The gross and microscopic examinations of the customary kind did not reveal evidence of hyperactivity in the adenoma. In fact, the general appearance is represented in the low-power photograph (Fig. 2) of a hæmatoxylin and eosin section, which is quite characteristic of the whole adenoma.

In the absence of the common criteria of thyroid overactivity such as have been mentioned previously in this paper, there remained the possibility that, in spite of this absence, the activity of some or all of the cells of the adenoma might be in excess of the normal, thus producing an excessive amount of active thyroid principle. The latter could then be the cause of the symptoms of hyperthyroidism, and still, locally in the adenoma, there might be an absence of cellular hyperplasia and no diminution in the amount of stainable colloid in the follicles.

To determine this point it becomes necessary to demonstrate, if possible, by histological methods evidences of increased cellular activity. For this purpose a technique was employed which demonstrates clearly and fairly easily the presence, in the cell cytoplasm, of structures commonly known as mitochondria. The functional significance of the latter has been considered in a recent summary on this subject by E. V. Cowdry,¹ to which reference should be made for a complete account of these structures. I may say briefly that the mitochondria are structures occurring in the cytoplasm of all cells. They occur in the form of granules, rods or filaments. Observations made upon living cells in tissue cultures have furthermore shown that they may change their form. They were first observed by Altmann,² and more recently their functional significance has been more accurately studied. In their solubilities and staining reactions they resemble phospholipins and to a lesser extent albumins. They are undoubtedly closely related to the life process of the protoplasm of every living cell, and there is ample evidence that mitochondria play an active and fundamental rôle in cell activity.

A few facts that support this view may be mentioned. They are present in the cells not only of animals, but also of plants. They are more abundant in the active stages of the life of the cell and diminish progressively in number as the cells become senile. This is exemplified in the cells of the different layers of the skin. In the deeper layer where cell division and growth are more rapid, the mitochondria are not numerous, while in the more superficial cells, those either dead or dying, the mitochondria are either very few in number or entirely absent. Moreover, the mitochondria decrease in number as one passes from nucleated to non-nucleated red blood cells. It is well known also that mitochondria are particularly abundant in immature embryonic cells, in which metabolic processes are very active. Romeis³ has found that mitochondria are very numerous in actively regenerating tissues. He used the term *plasmosomes*, a synonym for mitochondria. They have been observed, furthermore, to be increased in number in kidney cells after the administration of phloridzin. Other facts could be cited, which have been advanced by investigators to support the view that mitochondria participate in the processes involved in cell activity and metabolism. By some the mitochondria are said to be transformed into zymogen granules as in the pancreas, and thus to be the antecedents of the specific secretion of glandular cells.

In accordance with these facts it would seem probable that in glandular cells that are the site of increased secretory activity we should find in the cytoplasm an increased number of mitochondria over the normal. To determine this point a technique which has been devised by Bensley⁴ was applied

to the adenoma and to the adjoining normal thyroid tissue with the results to be described. Before discussing the latter I should like to mention a word in regard to this method. The tissue to be examined should be absolutely fresh, and placed in the fixation fluid in small pieces immediately after removal from the body. If this precaution is observed and the technical steps recommended by Bensley are carefully followed, no difficulty should be experienced in obtaining satisfactory results. The fixation fluid is an osmic-acid, bichromate of potash and acetic acid mixture, and the subsequent staining consists in the application, after mordanting with potassium permanganate, of acid fuchsin with a counter-stain of methyl-green. The sections should be less than 5 micra thick. The mitochondria are stained a brilliant red and are readily recognized, particularly with a sharp counter-stain such as methyl-green.

Now when the normal thyroid tissue adjoining the adenoma is studied after this technique has been applied, a picture resembling that illustrated in Fig. 3, as drawn by Miss E. Norris, is obtained. The mitochondria, staining a brilliant red in acid-fuchsin, appear in lower power magnification as small granules, but under the higher power oil-immersion lens they appear as short thick filaments or rods. They are scattered fairly uniformly throughout the cell cytoplasm which is rather scant in amount. In the more flattened cells the mitochondria are more abundant at either side of the nucleus, but in the cells provided with a greater amount of cytoplasm they occur also along the lumen border of the cell. Relatively rarely one sees cells in which the mitochondrial content is more abundant. In the space between the follicles, small aggregations of thyroid cells, without formation of acini but with the average number of mitochondria, are seen. The cytoplasm, scanty in amount, stains a faint green. The nuclei are vesicular in shape, stain faintly green, and often show the presence of nucleoli, which take on a darker green color.

The intrafollicular colloid stains homogeneously and appears light green which is often tinted a pink color, due to the amount of differentiation of the section in methyl-green or probably also to the age of the colloid. The latter, whenever present in the smaller, apparently younger follicles, is always greenish in color. No extrafollicular colloid was seen in the normal thyroid tissue.

If now we compare this picture with that obtained after applying precisely the same technique to the adenoma, results are obtained which are illustrated in Fig. 4. These appearances are quite characteristic of sections made from small blocks of tissue taken from numerous different areas in the adenoma. The mitochondria present essentially the same morphological features as in the normal gland. The strikingly greater abundance of the mitochondria everywhere in the sections of the adenoma, as compared with the normal gland, is at once apparent. This is true of practically all of the parenchymal cells regardless of whether these cells are tall columnar and contain a relatively abundant cytoplasm or whether they are flattened and poor in protoplasm. The cells themselves vary markedly in shape and size. Some are large

¹ Cowdry, E. V.: The General Functional Significance of Mitochondria. *Am. Jour. Anat.*, May, 1916, XIX.

² Altmann, R.: *Die Elementarorganismen*, 1890. Leipzig, Veit & Comp., p. 145.

³ Romeis, B.: *Das Verhalten der Plasmosomen bei der Regeneration*. *Anat. Anz.*, 1913, XLV, 1-19.

⁴ Bensley, R. R.: Studies on the Pancreas of the Guinea-pig. *Am. Jour. Anat.*, 1911, XII, 308.

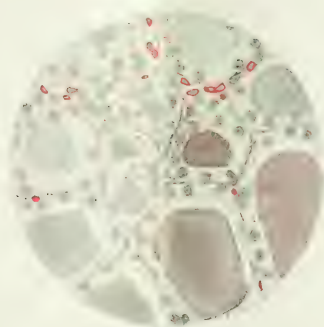


FIG. 3.—Drawing of section (4 mm. thickness) representative of the appearance of the normal right thyroid lobe adjacent to the fetal adenoma. Note the relatively small number of mitochondria in the thyroid cells. (Acetic-osmic-bichromate fixation. Acid-fuchsin-methyl green. $\times 390$. Oil immersion.)



FIG. 4.—Drawing of section (4 mm. thickness) of "fetal adenoma" in right thyroid lobe and isthmus, to show the relatively large numbers of mitochondria in the parenchymal cells as compared with the adjoining normal thyroid cells (cf. Fig. 3). Note also the large amount of extra-follicular colloid. $\times 390$. (Technique same as in Fig. 3.)

and columnar; the greater number are low and cuboidal; and others are very much thinned out by pressure of the colloid contained within the follicles. Even the cells of the last type, presenting much the same appearance as the atrophic cells of an inactive colloid goitre, are rich in mitochondria.

The nuclei are on the whole slightly larger and somewhat richer in chromatin. The staining characters of nuclei and cytoplasm are in general the same in each instance. The intra- and extra-follicular colloid stains a homogeneous light green color. In several of the latter, desquamated parenchymal cells are seen containing great numbers of mitochondria. In some areas outside of the follicles colloid is seen in rather large amounts. Here and there solid groups of thyroid cells are seen, with no indication of follicle formation and containing great numbers of mitochondria.

That analogous conditions are probably present in animal pathology was indicated to me recently in the study of a tumor of a dog's thyroid brought to me by G. B. Wislocki. A circumscribed encapsulated tumor, the size of a cherry, was found enclosed in the center of an otherwise normal-looking thyroid lobe. The findings in the gross and in the general microscopic examinations of the gland were much the same as those occurring in a somewhat similar case described and illustrated by Goodpasture and Wislocki,⁵ in their study of the relationship in dogs of old age to cell-overgrowth and cancer. In the present instance, however, there was no degeneration to be observed in the center of the adenoma. The latter was in all likelihood a hyperactive adenoma, for, as compared with the surrounding normal thyroid tissue, it contained in its parenchymal cells mitochondria in far greater number. Furthermore, there was in this case a moderate hyperplasia of the usual type. It would seem from this that there is reason for believing that hyperthyroidism symptoms might readily occur, in the dog as in man, in cases of similar pathological involvement of the thyroid gland.

In contradistinction to the case reported here, I have observed several instances of encapsulated thyroid adenomata, unassociated with symptoms of hyperthyroidism, and with no

increase, in fact rather a decrease, in the number of mitochondria present in the follicular cells. In three recent cases of thyroid adenomata associated with marked symptoms of hyperthyroidism, but without exophthalmos, the parenchymal cells have shown a great increase in the number of mitochondria in their cytoplasm. Another evidence, empirical perhaps, that the adenomata of this latter class are hyperactive, is shown by the subsidence of the symptoms of hyperthyroidism almost immediately after the surgical removal of this tissue so excessively rich in mitochondria.

It is evident then that a method or technique is needed that will give us the means for determining whether the individual thyroid cells are functionally hyperactive or not, for without it and with reliance placed solely upon the older criteria of hyperactivity as pointed out above, many clinical cases of hyperthyroidism cannot be correlated with the histological appearance or changes occurring in the thyroid gland. It is the purpose of this preliminary report to call attention to the value of, and the need for, finer cytological studies in determining glandular function, especially in a gland presenting so many variations in its pathological anatomy as the thyroid gland. It is further felt that in the study of the pathological anatomy of the thyroid gland, the mitochondria will prove to be a better index of thyroid activity than the histological criteria heretofore applied. Since the mitochondria occur normally in the thyroid cell, and since they are present in greatly increased numbers in the adenomata associated with symptoms of hyperthyroidism, it would seem probable that they are correlated with an overproduction of an otherwise normal secretion produced by the thyroid cell. It is interesting to speculate why exophthalmos is so rarely if ever associated with thyroid adenomata. It may be that there is a very different form of intoxication in the true Basedow's disease. In the latter the thyroid gland, just as in the case of the toxic adenomata, shows a marked increase in mitochondria over the normal. There are, however, several differences in these two conditions in the number, morphology, size and distribution of the mitochondria, a description of which will be given in a later report. Interesting results will undoubtedly be obtained when studies are made on the occurrence of mitochondria in hyperplasias and pathologic new-growths occurring elsewhere than in the thyroid gland.

⁵ Goodpasture, E. W., and Wislocki, G. B.: Old Age in Relation to Cell-overgrowth and Cancer. *Jour. Med. Research*, XXXIII, No. 3, p. 473.

RENAL DIABETES.¹

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AND

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From time to time there have appeared in medical literature reports of "renal diabetes." Under this term is understood a glycosuria which is the result of an abnormal permeability of the kidney to sugar. The kidney in this pathological state allows a small amount of sugar to escape constantly in the

urine, while the blood sugar maintains a normal level of between 0.07 and 0.11 per cent. The body has lost none of its power to utilize carbohydrate and hyperglycaemia is not found as it is in true diabetes mellitus. Consequently, an increase or decrease of the carbohydrate constituents of the diet has little effect on the percentage of sugar in the blood or the quantity excreted in the urine. These cases have none of the clinical

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manifestations of diabetes mellitus, due either to a diminished ability of the body to utilize glucose or to the presence of a hyperglycemia; there is no polydipsia, polyphagia or polyuria, no loss of weight or weakness, no pruritus or furunculosis, nor any other symptom of the disease. According to the present conception of this condition, it remains stationary, the glycosuria showing no tendency to increase, nor does diabetes mellitus develop from it; the subject continues in good health and without any abnormal symptoms or signs except a constant low-grade glycosuria. The data necessary for the diagnosis of renal diabetes are very few in number but sharply defined:

1. A glycosuria, maintained at a fairly constant level and not markedly affected by changes in the carbohydrate content of the food.

2. A normal percentage of blood sugar while the urine contains glucose.

From this description, it is evident that the term "renal diabetes" is a misnomer and that "renal glycosuria" would be more appropriate.

Thus far, very few cases of this interesting anomaly have been reported. Von Noorden,² in his monograph on diabetes mellitus, does not consider the symptom-complex of renal diabetes to be firmly established. His skepticism is no doubt due to the small number of cases on record. Allen,³ in his recent thorough summary, "Glycosuria and Diabetes," admits two cases, those of Bonninger⁴ and Tachau,⁵ as indisputable examples of this condition. Since that time, several other instances of apparent abnormal permeability of the kidney to glucose have been published. Bonninger⁶ observed a man, aged 37, who on life insurance examination two years previously had shown a glycosuria. After 10 days of irregular sugar excretion, probably influenced by severe alcoholic poisoning, the urine on 33 subsequent days was remarkably constant in its glucose content, which varied within the narrow limits of 0.1 to 0.5 per cent. These percentages were maintained on a carbohydrate-free diet as well as when the food contained an ample amount of the usual starches or included 100 gm. of dextrose or cane sugar. The urine collected in four or five specimens during the 24 hours for a period of eight days showed the same quantity of sugar (0.1 to 0.6 per cent) in each sample. The blood sugar was 0.08 per cent; some time later it was 0.06 per cent, and the urine which was voided before and after the latter determination contained 0.5 per cent of glucose. Bonninger⁷ subsequently reports that this case has been observed for six years (eight years since glycosuria was demonstrated by life insurance examination), that he still excretes small amounts of sugar, and is in perfect health. The son of the patient is also afflicted with renal diabetes.

This case furnishes a convincing illustration of the existence of renal diabetes, provided that the sugar excreted was glucose.

The blood sugar is normal, the glycosuria is constant and does not vary in direct proportion to the ingestion of carbohydrates, the disease is not progressive, and, finally, its hereditary character, upon which some authors have laid stress, is noted. The instances of this condition subsequently reported have shown that the intensity of the glycosuria is to a great extent, but not absolutely, independent of the carbohydrate intake. This is seen in our patient and is very evident in the following case, which was published by Tachau:⁸

E., aged 21, merchant, suffering with transient acute nephritis and gastro-enteritis following an excessive indulgence in fruit.

Days observed.	Diet.	Urinary glucose, gm. in 24 hours
4	Carbohydrate free	0
6	Mixed (158 to 250 gm. carbohydrate)	0
15	Mixed (124 to 412 gm. carbohydrate)	1.1 to 6.0
3	Mixed plus 100 gm. dextrose.....	0.6 to 4.2

The days are grouped according to diet and the presence or absence of glycosuria and are not placed in chronological order.

Blood sugar determinations in per cent:

Fasting	0.085 and 0.086
After breakfast	0.061
1 hour after 100 gm. dextrose.....	0.076, 0.109 and 0.082

The absence of glycosuria on some of these days can probably be explained by the fact that the level of the blood sugar varied at times and was on occasion depressed below the kidney threshold for this substance. It is known from the publications of Jacobson,⁹ Strouse¹⁰ and others, that there is a distinct rise of the blood sugar after meals. Since there is a universal tendency to hyperglycemia after meals, slight fluctuations in glycosuria are to be expected in typical instances of renal diabetes. The criterion of an absolutely constant quantity of urinary dextrose cannot, therefore, be insisted on.

Other cases, which are considered to be true examples of renal diabetes have been brought forward by Graham¹¹ and de Langen.¹² The reports of Frank,¹³ Rogue and Chalié¹⁴ and Solomon¹⁵ either lack sufficient data to establish the diagnosis of renal diabetes, or, as in some of Solomon's patients, appear to belong to cases of mild diabetes mellitus. Frank's exposition of increased renal permeability during pregnancy and after poisoning with mercury, uranium, chromium and cantharidin confirms the work of many investigators and furnishes suggestive evidence of the existence of a permanent renal glycosuria.

The question presents itself, why the renal barrier to sugar should be only slightly depressed, causing a renal glycosuria of such mild degree, and why the kidney threshold should not be more markedly lowered in some individuals, and conditions re-

⁸ Tachau: *L. c.*

⁹ Jacobson: *Biochem. Ztschr.*, 1913, LVI, 471.

¹⁰ Strouse, Stein and Wiseley: *Bull. Johns Hopkins Hosp.*, 1915, XXVI, 211.

¹¹ Graham: *Jour. Physiol.*, 1915, XLIX, p. XLVI (Proceedings).

¹² de Langen: *Berl. klin. Wchnschr.*, 1914, LI, 1792.

¹³ Frank: *Arch. f. exper. Path. u. Pharmacol.*, 1913, LXXII, 387.

¹⁴ Rogue and Chalié: *Arch. d. mal. de l'apparat digest.*, 1912, VI, 661.

¹⁵ Solomon: *Deutsche Med. Wchnschr.*, 1914, XL, 217.

² Von Noorden: *Die Zuckerkrankheit*, Berlin, 1912, S. 37.

Allen: *Glycosuria and Diabetes*, Boston, 1913, p. 544.

⁴ Bonninger: *Deutsche Med. Wchnschr.*, 1908, XXXIV, 780.

⁵ Tachau: *Deutsch. Arch. f. klin. Med.*, 1911, CIV, 448.

⁶ Bonninger: *L. c.*

⁷ Bonninger: *Verhandl. d. Cong. f. inn. Med.*, 1913, XXX, 178.

sembling phlorizin glycosuria be found? It is very likely that such instances do occur, but have hitherto usually been confounded with true diabetes. One example of such a case, however, is on record. Galambos¹⁶ cites the following data of a patient, a man 50 years old, who has suffered with polyuria and polydipsia ever since he can remember. Observation was carried on over a period of 21 days during which time the glycosuria varied between 66 and 198 gm., and the concentration of urinary dextrose between 2.6 and 7.4 per cent. The carbohydrate content of the diet was between 50 and 354 gm. Frequent collections of urine in this case showed a marked constancy in the hourly excretion of glucose; the administration of 150 gm. of dextrose did not result in any marked deviation from this regularity; on a day during which the 24-hour specimen was collected in five separate portions, it was found, on making the proper calculations, that 6.4, 4.4, 6.6, 4.8 and 6.6 gm. of glucose were excreted per hour in the various periods. These quantities are very much larger than in any of the cases hitherto reported. The blood sugar values, in per cent, were: During fasting, 0.09 and 0.05; 1½ hours after oatmeal feeding, 0.07; and 1½ hours after taking 100 gm. of dextrose, 0.17. The last figure is slightly above that which would be expected in most normal individuals,¹⁷ but is not sufficiently high to invalidate the conclusion that this case is one of renal diabetes. There was a considerable degree of acidosis. This is only to be expected with the enormous losses of glucose in the urine; the carbohydrate balance between intake and output was often negative. This case, therefore, illustrates the possibility of a renal diabetes of severe type, a type which approaches in its characteristics the phenomena observed in phlorizin poisoning. Whether this patient presents an extremely rare anomaly or a condition of more frequent occurrence than has hitherto been suspected can be determined only through further study.

The number of published cases of renal glycosuria or diabetes which stand the test of closer investigation have been relatively few. The following record may, therefore, be of interest:

W. P. W., Medical History No. 34774, male, white, age 29, born in the United States, a station agent, descended from Anglo-Saxon ancestry.

Family History.—Father (aged 60), mother (aged 50), 1 brother and 4 sisters are all alive and in good health; one sister died of erysipelas. With the exception of marked obesity in one grandmother and several of her sisters, there is no history of hereditary disease; diabetes mellitus, heart trouble, kidney disease, apoplexy, gout, exophthalmic goitre and tuberculosis have never been found in the patient's family.

Habits.—Smokes 5 to 6 pipes a day; does not use alcohol; eats a considerable amount of bread but no excess of sweets.

Past History.—Measles and whooping cough in childhood, malaria 18 years ago, pneumonia 17 years ago, varicella, complicated by otitis media on the right side, 15 years ago. Venereal infection is denied.

Present History.—Three years ago passed a life insurance examination. This is the only urinary test remembered, until six

weeks ago, when the patient applied to his physician for relief from backache. At that time, a glycosuria was demonstrated. The backache cleared up shortly; the glycosuria persisted in spite of a restriction of the carbohydrates in the food. There never have been any other symptoms pointing to diabetes mellitus with the exception of transient paresthesia of the fingers (no loss of weight or strength, no polyuria, polydipsia or polyphagia, no skin involvement—pruritus, furunculosis or other condition—no muscular cramps, no pains in the extremities); there have been no evidences of pancreatic disease (no pain in the epigastrium, no fatty diarrhea); all indications of exophthalmic goitre have been completely lacking at all times (no exophthalmos, no thyroid enlargement, no vomiting, nervousness, cardiac palpitation or diarrhea); there have been no signs of acromegaly or gigantism pointing to hypophyseal involvement; there has been no history of a renal lesion (no headache, visual disturbance, dyspnea, vertigo, edema or albuminuria); there has never been any skin pigmentation to suggest a cirrhosis of the pancreas and liver, that is, a hemachromatosis.

For the last two or three years there has been a tendency to increased frequency of urination during the day but not at night. The quantities voided have apparently not exceeded normal. This is evidently a pollakiuria rather than a polyuria, which is borne out by the ward observations which will be detailed further on.

There has been a slight chronic cough associated with a moderate nasal catarrh and mouth breathing. There have been no night sweats, hemoptysis or "pleuritic pain."

Present Complaint.—The patient feels perfectly well and would not believe himself sick were it not for the persistent, "sugar in the urine."

Physical Examination.—Height 5 feet 9¾ inches, weight 152 pounds; appears to be in the best of health and spirits; the skin and mucous membranes are not pigmented, their color is normal, they are as moist as those of a normal individual. The pupils are equal and react to light and accommodation; von Graefe's sign is absent. The pharynx is injected and there is a moderate degree of nasal obstruction, as indicated by persistent mouth breathing. The tonsils are not enlarged or inflamed. There is no pyorrhea alveolaris. The thyroid is barely palpable. The pulse rate averages 75; the pulse is regular in force and frequency and of normal volume. The radial artery can be rolled under the palpating finger, but is soft and elastic. The temperature is normal. The respiratory rate ranges from 16 to 24. The systolic blood pressure is 140, the diastolic 80. The heart's apex beat cannot be seen, it is barely palpable in the fifth interspace, 10 cm. to the left of the median line; the character of the apex impulse is a normal one; there are no thrills over the precordium; the area of relative cardiac dullness extends 3.5 cm. to the right of the mid-line in the fourth space, and 10.5 cm. to the left in the fifth; the heart sounds reveal no murmurs, the second sound over the aortic area is somewhat intensified and is louder than the pulmonic second sound. The lungs are normal except for slight dullness and somewhat prolonged expiration in the right supraspinous fossa, and at times a few dry rales, after coughing, over the same area. The liver and spleen are not palpable and there are no areas of tenderness or increased resistance over the abdomen. The patellar reflexes are very active. There is no edema of the face, back or extremities. On the left thigh there is a small eczematous patch furrowed by scratch marks. The superficial lymph nodes are not enlarged. The hemoglobin is 100 per cent (Sahli), the red blood cells are 4,600,000 and the white blood cells are 8450 per cu. mm. The Wassermann test is negative. The urine on admission is clear, of reddish yellow color, specific gravity 1035, acid in reaction, negative for albumin, gives a distinct reaction for sugar, and on microscopic examination yields no casts or red blood cells; the qualitative tests for acetone and diacetic acid are negative; the phthalein test shows an excretion of 42 per cent in two hours; Ambard's constant determined at various times is 0.07, 0.11, 0.08, 0.10.

¹⁶ Galambos: Deutsche Med. Wchnschr., 1914, XL, 1301.

¹⁷ Jacobson: L. c.

Impression.—The presence of glycosuria was well established. The urine gave a positive reaction with both the quantitative and qualitative Fehling-Benedict reagent, yielded gas on fermentation with yeast, and the unfermented urine rotated the polariscope to the right. The nature of the glycosuria will be subsequently discussed. There may have been a healed tubercular lesion at the right apex; impaired resonance, slightly prolonged expiration and inconstant râles in this region are not pathognomonic of a tuberculous focus; it is certain that in the absence of fever, sputum, night sweats, chills and loss of weight an active process is not probable and therefore of no significance in explaining the glycosuria. Of equally little importance is the nasal obstruction and pharyngitis. The kidneys are anatomically intact as far as the physical and urinary signs are concerned; the functional tests of these organs, however, reveal some impairment as shown by a slightly diminished "phthalein excretion and an Ambard's constant barely within what has been in our experience the upper normal figure. The connection between such a diminished kidney function and a possible renal diabetes are of extreme interest. The small eczematous patch in this case could not be regarded as a complication of diabetes mellitus, since the hyperglycemia, which is the direct etiological factor of such a condition, was lacking.

The urinary nitrogen was determined by the Kjeldahl process, the ammonia according to Folin,¹⁹ the glucose by Benedict's modification of Fehling's method,²⁰ the acid bodies by Shaffer's procedure.²⁰ The method of Lewis and Benedict²¹ was used in estimating the blood sugar.

In this case the blood sugar levels were normal, though the urine voided at the same time that the blood specimens were taken invariably contained glucose. The first three determinations showed a slight tendency towards a hyperglycemia, 0.11 to 0.13 per cent; these figures are probably too high, since, as noted in the foot-note to Table 1, the standard used to obtain them was at fault. This supposition is confirmed by the fact that the 18 subsequent results, unless they were carried out at times when abnormal amounts of sugar had been added to the diet, were strictly within normal limits, being either 0.09 per cent or less. It is known that the level of blood sugar in diabetes mellitus after the ingestion of glucose assumes a course different from that in normal individuals and presumably in those afflicted with a renal diabetes. In the present instance (Table 2) after the ingestion of 100 gm. of glucose, a hyperglycemia of 0.15 per cent was evident within 35 minutes; two hours and five minutes after the experiment was begun, the blood sugar level returned to normal and subsequently became depressed below this figure. This is almost an exact duplicate of the curve which Jacobson²² produced in normal persons under similar circumstances—a hyperglycemia of an average duration of two hours, a rise of the blood sugar, which reaches its maximum in about 30 minutes, and in many cases a hypoglycemia following the hyperglycemia. The maximum blood sugar values obtained by this author after this test varied from 0.12 to 0.23 per cent. In diabetes Jacobson found somewhat the same results after the ingestion of 50 gm. of bread and it

is only fair to assume that the figures would have been very much exaggerated had 100 gm. of glucose been taken instead. Table 3 demonstrates very clearly how the urine in the present case invariably contains sugar, rising as high as 2.2 per cent while the blood sugar maintains a normal level.

The urinary sugar is considerably reduced by restricting the carbohydrates of the diet, but is completely absent only after six days of starvation (Table 1) and reappears with a minimum amount of food. In diabetic patients exhibiting 11 to 13 gm. of glucose in the urine on a mixed diet, a sugar-free state has regularly been obtained after one or two days of starvation. That the amount of dextrose excreted is somewhat dependent on the diet, but to a very much less degree than in true diabetes, is seen in this instance as well as in some of the cases previously reported. Furthermore, it may be noted from Tables 1 and 3 that glycosuria was below 12 gm. on all the days when the diet was restricted, but reached 30 gm. when the carbohydrate intake was raised. The two-hourly specimens (Table 3) showed a marked constancy in the amount of sugar eliminated during each day. Here again the amounts varied to some extent in direct proportion with the starchy content of the food. This is accentuated in the urinary collections of October 20-21 and October 21-22, in which 0.5 gm. of glucose was excreted per hour at night, as compared with 0.8 to 2.7 gm. during the day. The direct effect of raising the blood sugar by carbohydrates is thus shown, since the kidney which is permeable to glucose at a subnormal level acts as an indicator of a normal blood sugar increase after meals.

The intensity of the acidosis during starvation, as shown by the quantitative and qualitative tests for the acid substances and the ammonia nitrogen ratio, is moderate in extent. It is difficult to interpret such a finding as indicative either of a true diabetes mellitus or of its absence. That acidosis occurs in normal individuals on carbohydrate as well as on total starvation, is a well-known fact. The observations made on fasting diabetics have shown that in some individuals the acidosis disappears rather promptly, while in others, especially the obese cases, it does not.²³ This has also been our experience. The interpretation of acidosis in fasting diabetics is especially obscure, not only because different patients show varying results due to their own constitutional peculiarities, but also because the procedure of fasting in diabetes, as practiced up to the present, has demanded the administration of broth, alcohol and bicarbonate of soda, all of which may either increase or diminish the excretion of acid substances. The studies in this instance would, therefore, make it possible to place this patient either in the category of those suffering with diabetes mellitus or those presenting a normal carbohydrate metabolism.

An attempt was made in our case to check the renal glycosuria by means of calcium chloride. Injections of this drug diminish the permeability of the kidney to glucose.²⁴ Fifteen

¹⁹ Folin: *Ztschr. f. physiol. Chem.*, 1902, XXXVII, 161.

²⁰ Benedict: *Jour. Biol. Chem.*, 1911, IX, 57.

²¹ Shaffer: *Jour. Biol. Chem.*, 1908, V, 211.

²² Lewis and Benedict: *Jour. Biol. Chem.*, 1915, XX, 61.

²³ Jacobson: *L. c.*

²⁴ Joslin: *Am. Jour. Med. Sc.*, 1915, CL, 485.

Allen: *New York State Jour. Med.*, 1915, XV, 320.

²⁵ Underhill and Closson: *Am. Jour. Physiol.*, XV, 321.

TABLE 1. URINE ANALYSES, BLOOD SUGAR DETERMINATIONS AND DIET.

Date.	Volume in cc.	Total N., gm.	Ammonia, gm.	Urine 24 hours.		Ammonia N. as per cent of total N.	4 Acetone.	4 Diacetone acid.	Total acid substances as β -oxybutyric acid, gm.	Glucose.		Blood sugar, per cent.	Diet :				Weight, lbs.	Remarks.
				Per cent.	gms.					Protein, gm.	Fat, gm.		Carbohydrate, gm.	Calories.				
Sept. 29-30	630	6.43	0.56	7.2	0	0	0	0	2.07	13.1	+	+	+	+	152	"Ward Light" diet.
30-1	830	6.76	0.50	6.0	0	0	0	0	1.34	11.1	*0.13	+	+	+	+	" " "
Oct. 1-2	750	8.34	0.58	5.8	0	0	0	0	1.58	11.9	0	0	0	0	Starvation.
2-3	455	9.93	0.52	4.4	++	+	+	+	2.33	1.10	6.1	0	0	0	0	" "
3-4	550	12.12	0.76	5.2	++++	+++	+++	+++	2.87	0.90	5.0	0	0	0	0	144	" "
4-5	485	10.13	0.97	7.9	+++++	+++	+++	+++	2.54	0.56	2.7	*0.11	0	0	0	0	" "
5-6	700	13.37	1.64	10.2	+++++	+++	+++	+++	5.54	0.10	0.7	0	0	0	0	" "
6-7	590	10.77	1.56	12.0	+++++	+++	+++	+++	4.28	0.36	2.1	*0.11	0	0	0	0	138	" "
7-8	455	8.11	1.13	11.6	+++++	+++	+++	+++	3.80	0.0	0.0	12	0	3	62	138	" "
8-9	580	9.68	1.39	11.9	+++++	+++	+++	+++	2.49	Trace.	Trace.	21	14	7	245	136	" "
9-10	645	10.30	1.31	10.5	+++	++	++	++	1.82	0.66	4.3	23	16	14	301	137	" "
10-11	550	7.70	0.99	10.5	+++	++	++	++	1.59	0.63	3.5	23	19	14	328	137	" "
11-12	785	9.64	1.36	11.6	+++++	+++	+++	+++	3.52	0.66	5.2	25	16	14	309	138	" "
12-13	1495	5.17	1.01	16.2	+++++	+++	+++	+++	1.06	0.80	11.9	0.09	25	16	14	309	138	" "
13-14	2378	++	+	+	+	0.93	0.27	6.5	78	44	15	791	137	" "
14-15	1635	10.43	1.98	15.7	+	+	+	+	+	+	101	151	15	1880	137	" "
15-16	1496	15.13	+	+	+	+	0.98	14.7	0.09	127	133	28	1846	" "
16-17	1373	12.91	+	0	0	0	1.21	16.6	0.09	144	145	94	2314	138	" "
17-18	1440	13.70	1.14	6.9	+	0	0	0	1.60	23.0	0.09	139	216	126	3095	138	" "
18-19	1230	11.79	1.23	8.7	0	0	0	0	1.20	14.8	0.09	140	234	130	3283	141	" "
19-20	1333	0	0	0	0	1.94	25.9	112	226	148	3168	141	" "
20-21	1348	14.29	1.91	11.1	0	0	0	0	1.71	23.0	0.08	147	235	270	3896	143	Glucose 150 gm. (50 gm. with each meal).
21-22	1670	15.53	1.31	7.0	0	0	0	0	1.63	27.3	123	155	99	2352	143	" "
22-23	1770	13.26	1.14	7.1	0	0	0	0	0.81	14.4	96	130	113	2066	141	" "
23-24	1410	13.67	0.79	4.8	0	0	0	0	0.88	12.3	108	118	67	1815	" "
24-25	1170	12.75	0.57	3.7	0	0	0	0	0.98	11.5	124	125	60	1917	" "
25-26	2315	18.90	0.98	4.3	0	0	0	0	1.29	30.0	0.08	110	130	148	2267	Glucose 100 gm. with midday meal.

* The first three blood sugar determinations were made with a standard that evidently yielded too high results. A new and carefully controlled standard in the subsequent determinations invariably gave lower readings, even after the administration of dextrose.

† Legal's reaction for acetone and Gerhardt's ferric chloride test for diacetic acid were used, + indicates a trace, ++++ a maximal reaction.

‡ No alcohol was given at any time.

TABLE 2. BLOOD SUGAR DETERMINATIONS AND DEGREE OF GLYCOSURIA AFTER A MEAL CONTAINING 100 GRAMS OF DEXTROSE.

OCTOBER 25. A MEAL CONTAINING 100 GRAMS DEXTROSE.

Blood Sugar, per cent.....	Before the Meal.						After the Meal.					
	Urine Glucose, per cent.....						35 min.	1 hr. 10 min.	1 hr. 35 min.	2 hrs. 5 min.	2 hrs. 40 min.	3 hrs. 15 min.
.....	0.09	0.15	0.12	0.12	0.09	0.07	0.15	0.10	0.12	0.09	0.07	0.06
.....	0.06

TABLE 3. HOURLY GLUCOSE EXCRETIONS AND THEIR RELATIONS TO DIET AND BLOOD SUGAR.

OCTOBER 13-14										OCTOBER 19-20														
		Urine.		Blood sugar.		Diet.				Urine.		Blood sugar.		Diet.										
Date.	Time.	Glucose.				Time.	Per cent.	Time.	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Time.	Per cent.	Time.	Protein, gm.	Fat, gm.	Carbohydrate, gm.							
		cc.	Per cent.	Total gm.	Gm. per hour.																			
Oct. 13-14 . . Day.	8-10	845	0.16	1.4	0.7	6 13	21	3	Oct. 19-20 . . Day.	6-8	8102	1.96	2.0	1.0	6 39	82	61		
	10-12	370	0.14	0.5	0.3	10 12	7	1		8-10	116	1.78	2.0	1.0			
	12-2	265	0.24	0.6	0.3	12 33	8	6		10-12	108	1.51	1.6	0.8	10 2	0	0		
	2-4	275	0.16	0.4	0.2		12-2	2196	1.76	3.4	1.7	12 25	72	55		
	4-6	1168	0.38	0.6	0.3	5 20	18	5		2-4	4170	1.61	2.7	1.4			
	6-8	1130	0.59	0.8	0.4		4-6	98	2.08	2.0	1.0	5 46	72	32		
	8-8	325	0.64	2.1	0.2		6-8	888	2.94	2.5	1.3			
	Oct. 15-16 . . Day.	6-8	8133	0.69	0.9	0.5	6 29	55	6		Oct. 20-21 . . Day.	8-8	6455	2.18	9.9	1.0	
		8-10	10220	0.79	1.8	0.9	9 0.09	8 29	55	6			6-8	8122	2.3	2.8	1.4	5.50	0.08	6 36	78	96
		10-12	10164	0.49	0.8	0.4	10 12	6	1			8-10	10132	1.2	1.6	0.8	9	0.08	
12-2		2213	0.66	1.4	0.7	12 51	31	7	10-12	1236		1.6	2.2	1.1	10 2	0	0		
2-4		4128	1.08	1.4	0.7	12-2	2176		2.3	4.0	2.0	1	0.11	12 64	71	90		
4-6		97	1.50	1.5	0.8	4 0.09	5 35	42	14	2-4	4114	1.8		2.0	1.0				
6-8		8131	1.20	1.6	0.8	4-6	6172		1.3	2.2	1.1	5 45	86	85		
8-8		6410	1.25	5.2	0.5	6-8	8106		2.2	2.3	1.2	7	0.08			
Oct. 16-17 . . Day.		8-10	882	0.84	0.7	0.4	6 31	60	31	Oct. 21-22 . . Day.		8-8	8390	1.5	5.9	0.5	
		10-12	109	1.09	1.8	0.9	9 0.09	8 31	60	31			8-10	10280	1.92	5.4	2.7	6 33	71	29
	12-2	1216	0.72	1.8	0.9	10 2	1	0	10-12		12245	1.25	3.1	1.6			
	2-4	2290	1.08	3.1	1.6	12 75	42	33	12-2		2255	1.56	4.0	2.0	10 5	0	1		
	2-4	4144	1.35	2.0	1.0	2-4		4190	1.52	2.9	1.5	12 58	43	24		
	4-6	6110	1.66	1.8	0.9	5 36	42	30	4-6		6160	1.64	2.7	1.4			
	6-8	834	2.22	0.8	0.4	6-8		8140	2.27	3.2	1.6	5 27	41	15		
	8-8	6197	2.38	4.7	0.5	8-8		8100	1.51	6.2	0.5			

* 50 gm. carbohydrate given as dextrose.

grams of calcium chloride by mouth on October 26, and 24 gm. on October 27 and on October 28, had no effect in reducing the sugar output. Further experiments in this direction were contemplated but could not be carried out because of the limited stay of the patient in the hospital.

SUMMARY.

From these studies it becomes apparent that this patient showed glycosuria, but none of the other abnormalities characteristic of an impaired carbohydrate metabolism. This case, therefore, may be added to the small list of those that point to the existence of a so-called renal diabetes or renal glycosuria. The slightly diminished phenolsulphonephthalein excretion, the slight elevation of Ambard's constant above the normal, as well as the glycosuria, point to a depressed kidney function. The absence of any further subjective or objective signs, past or present, leads to the conclusion that a renal glycosuria is an interesting anomaly, but of no importance to the organism as a whole.

The question of prognosis in this condition is the most important problem which remains to be solved. It is well known that instances of true diabetes may persist for years without

changing from a mild to a severe type in spite of the lack of any systematic efforts at dietary restriction, thus resembling renal glycosuria. It is not certain that what is termed renal diabetes may not develop into diabetes mellitus, especially since comparatively little is known of the early stages of true diabetes. The number of cases of renal glycosuria thus far observed has been small and none of them has been followed for a sufficient length of time to ascertain whether renal diabetes is congenital, and not an acquired anomaly, and whether it may persist indefinitely without changing its characteristics.

The intensity of renal glycosuria should vary with the degree of kidney permeability to dextrose. With a threshold only slightly depressed, an intermittent glycosuria often of an apparently unexplained origin may be present; with a very marked depression, changes approximating the conditions found in phlorhizin poisoning should develop. Intermediary degrees of kidney involvement should have glycosurias of corresponding intensity. If the present ideas of the relations of a diminished kidney threshold for sugar are true, all the grades of intensity indicated should be demonstrated in the course of time.

BILATERAL AND COMPLETE TRIGEMINAL PARALYSIS WITHOUT INVOLVEMENT OF OTHER CRANIAL NERVES.*

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The anatomical relations of the trigeminal nerve as it emerges from the pons, its short intracranial course, and the protected position of its ganglion within the dural sheath suggest a probable explanation for the frequency with which this nerve escapes in diseases of the cerebral meninges.

Different opinions have been expressed, however, concerning the incidence of syphilitic affections of the fifth nerve, and Uthoff¹ claims that this nerve is involved in 14 per cent of all cases of cerebral syphilis. Forster² states that neuralgic disturbances are not uncommon, and that motor and sensory paralyzes have been observed. Oppenheim³ has also seen involvement of the motor root in one case, and von Ziemssen⁴ records a case with sensory changes, implication of other cranial nerves, and motor paralysis. In Lowenfeld's⁵ case, there was sudden isolated paralysis of the muscles of mastication upon one side, and Nonne⁶ has frequently observed syphilitic trigeminal affections, but usually in association with other cranial nerve symptoms. Hutchinson⁷ makes the surprising statement that he has "scarcely seen paralysis of the fifth nerve except as the result of syphilis"; and, although only one fifth nerve is affected, "it shows no tendency to become complicated by involvement of other cranial nerves." He has, however, observed two cases in which both trigeminal nerves were affected.

Unilateral motor paralysis has been observed in two cases by Spiller and Camp.⁸ Sensory changes in the trigeminal area were not present, but in one case associated hemiparesis and bilateral oculomotor paralysis were noted. In the second case, fibrillary tremor of the right masseter muscle had been noted and there was a history of pain in the right trigeminal area; but the patient's condition was such that a satisfactory sensory examination could not be made. Other cranial nerves were not involved, but there was a recent right hemiplegia discovered at autopsy to be due to meningitis and temporal lobe softening, and the pontile and spinal tracts of the fifth nerve were degenerated.

Although various combinations of symptoms have been described in syphilitic affections of the trigeminal nerve, there are certain features of the disease which are more or less characteristic: The more common symptoms are confined to sensory disturbances in one or two branches of the nerve, and rarely involve all three branches; the affection is almost always unilateral and associated with implication of other cranial nerves; the motor fibers are rarely affected; complete motor and sensory paralysis is rare even when other nerves are involved, and extremely rare as an isolated paralysis; and lastly, the disease is sometimes bilateral.

Complete syphilitic paralysis of the fifth nerve has been described by Neiding⁹ who refers to a similar observation by Kuttner. In Neiding's case, the symptoms, which were con-

* Read before the Philadelphia Neurological Society, February 25; and before the Baltimore Neurological Society, March 17, 1916.

lined to the right trigeminal area, were attributed to syphilitic disease of the Gasserian ganglion. Other cranial nerves were not affected and there was no evidence of involvement of the central nervous system. Complete insensibility and motor paralysis were present upon the affected side, and taste was lost upon the anterior portion of the tongue. Examination of the blood showed a strongly positive Wassermann reaction, but a study of the spinal fluid was not made. After three months of active specific treatment there was marked improvement and the patient was considered clinically well.

Total syphilitic paralysis of the trigeminal nerve, either alone or in combination with other cranial nerves, is of sufficient importance to make even a clinical record of such cases valuable; and the peculiar syndrome observed in the patient whose illness is related in this paper is, I believe, unique in medical literature.

F. M., a male, unmarried, aged 29, who complained of "syphilis," was admitted to the service of Dr. H. H. Young at the Johns Hopkins Hospital, January 19, 1915. The family history is unimportant, and there is a personal history of the usual diseases of childhood, several attacks of malaria, and at the age of 19 gonorrhœa complicated by a double epididymitis. Six weeks ago, December 4, 1914, he noticed a sore upon the left side of the foreskin which was diagnosed as a chancre, but for which he received only local treatment from his family physician. The primary lesion healed, and the patient considered himself well until January 9, 1915, when he began to complain of severe headaches, sore throat and a profuse skin eruption.

Examination upon admission to the hospital shows the presence of a hard chancre on the foreskin slightly to the left of the median line. Its center is covered by a small scab, beyond the edges of which there is an indurated area, measuring 1 x 2 cm. The inguinal glands are indurated and enlarged, and over the trunk and forearms there is a maculo-papular eruption.

Salvarsan, 0.6 gm., was administered intravenously, January 19, 1915; it was followed by a somewhat severe constitutional reaction. A second dose, of 0.6 gm., was administered January 26, to which he reacted only slightly. Business affairs called the patient away from Baltimore, and on February 2, without receiving further injections of salvarsan, he left for Porto Rico, with directions for taking "mixed treatment" by the mouth. The treatment was faithfully adhered to during his absence, until the following symptoms made their appearance.

Upon returning from a long automobile ride, March 8, 1915, three months after the primary lesion, he complained of ringing in both ears and severe headache. The next morning these symptoms had subsided, but after another long drive he went to bed because of a return of the intense headache associated with a chill, fever, nausea and vomiting. He was treated for "la grippe" for three or four days, after which all of the symptoms disappeared except the headache, which persisted and gradually became more intense; there was also a severe pain in the left side of the face "resembling facial neuralgia."

These neuralgic attacks continued until about March 14, when the patient noticed that the entire left side of the face felt numb, and chewing upon this side was difficult. Numbness in this region was so pronounced that movements were not fully appreciated, and he felt, when smiling, as if the face were drawn to the right side; but when this act was performed before a mirror he could notice no difference in the movements of the two sides of the face. Six days later, March 20, the right side of the face became slightly numb, without, however, any preceding pain, and it was almost impossible to masticate anything solid. Within two days the condition had so progressed that the entire front of

the head and both sides of the face were completely numb, and it was impossible to chew or even close the jaws. There has been no difficulty in the movements of the eyes or lids, nor is there a history of diplopia. Taste, swallowing, speech and movements of the tongue have not been impaired, and control of the arms, legs and sphincters has not been disturbed.

The patient became alarmed about his condition and decided to return to Baltimore, where he arrived March 30, and was admitted for the second time to the service of Dr. Young, who, on April 3, asked me to see the patient, when the above history was obtained. At this visit it was also learned that headache, nausea and vomiting, which had been prominent symptoms during the journey to Baltimore, since admission, had been less frequent; but that within the past two days he had experienced severe pain in the right thigh and difficulty in moving the right foot.

Physical examination by Dr. Cameron reveals no abnormality in the thorax or abdomen, and a laboratory report upon the blood and urine states that in the former there is a leucocyte count of 13,600, and that in the latter sugar and albumin are not detected. Since admission the temperature has varied from 99 to 101.4° F.

Examination of the nervous system is as follows: The patient is lying in bed with the mouth partly open, and is unable to close it when requested to do so. He looks ill, and complains of headache and pain in the face.

There are no subjective disturbances of the olfactory nerve, and when tests are made with valerian and oil of cloves, these substances are correctly named.

There is no disturbance of vision and the optic disc in each eye is of good color, the margins are well defined, the veins are not engorged, and the lamina cribrosa is visible.

Both pupils are slightly dilated, but equally so, and respond promptly to light, directly and consensually, and during accommodation. The extrinsic ocular muscles act normally in all movements of the eyes, and there is no nystagmus or strabismus. The left upper lid shows slight ptosis and there is consequent narrowing of the left palpebral aperture. It is stated, however, that this condition has existed since birth, and that it has not increased since the onset of the present illness. Movement of the upper lid is unimpaired.

The Fifth Nerve.—The patient complains of almost constant headache, pain in both ears, and numbness of the entire face. Objectively, there is complete loss of tactile, thermic and pain sense in the entire sensory area of both trigeminal nerves, except that in the distribution of the left maxillary nerve a pinpoint is occasionally recognized as such, although it does not produce a sensation of pain. Corneal sensibility is completely lost upon both sides, and when the eyes are closed, irritation of the nasal and buccal mucous membranes produces no response from either side, nor is the patient cognizant of what is being done. All forms of sensibility, except deep pressure, are lost upon both sides of the tongue in its anterior portion.

The motor portion of each fifth nerve is completely paralyzed and the lower jaw hangs drooping from its articulation, and cannot be closed voluntarily or moved in either lateral direction (Fig. 1). Tremor of the temporal and masseter muscles is not observed, but these muscles, upon both sides, fail to respond to faradic stimulation, and their reaction to the galvanic current is slow and lazy.

At rest the face is symmetrical and the naso-labial folds are of about equal intensity. In wrinkling of the brow, frowning, closing the eyes, and showing the teeth, the movements are equally well performed upon the two sides (Fig. 2). Taste, when tested with solutions of sugar, salt, acetic acid, and quinine, shows no impairment upon either side of the tongue, anteriorly or posteriorly.

A watch is heard slightly better with the right than with the left ear; and, because of this auditory defect, the patient was later referred to Dr. Jas. Bordley, who examined the ears and reported

that moist eczema was present in both external auditory canals. The vestibular portion of the eighth nerve was not examined minutely, but there were no definite subjective or objective evidences of disturbance in this division of the nerve.

There has been no difficulty with speech or in swallowing except that due to inability to move the lower jaw; and fluids do not regurgitate. The soft palate, although insensitive upon its oral surface, moves equally well on the two sides when saying "Ah," and the palatine muscles respond promptly to faradic and galvanic stimulation. The sternomastoid muscles and the trapezeii function normally and show no weakness or atrophy upon either side.

The tongue is protruded promptly and in the median line. It is slightly tremulous, but is under good control; the motor power is not diminished, and the response to both forms of electrical stimulation is prompt and vigorous.

A jaw-jerk is not obtained. The biceps and triceps tendon jerks are easily obtained and are equally active upon the two sides. Both knee-jerks are slightly hyperactive, and the left is greater than the right. The tendon Achillis jerks are present, but this reflex is more active at the right ankle. There is no ankle or patellar clonus. The epigastric, abdominal and cremasteric reflexes are equally active upon the two sides. Plantar stimulation and decending tibial irritation produce plantar flexion of the great toe upon each side.

There is no evidence of ataxia, weakness, or loss of voluntary control in either upper extremity, and sensation in the arms is normal. When standing with the feet together and the eyes closed, there is some unsteadiness; but the heel-tibial test is accurately performed with either leg. Walking is slightly impaired because of pain in the right leg and difficulty in flexing the right foot, which gives the characteristic "steppage" quality to the gait. Motor power in both legs is well preserved, except that upon the right side there is weakness in the tibial and peroneal group of muscles, and these muscles show diminished excitability to both forms of electrical stimulation and respond slowly to the galvanic current. Deep pressure over the right peroneal nerve is definitely painful, and there is moderate diminution of cutaneous sensibility in the area innervated by this nerve. Sensory changes other than those already noted in connection with the head and outer portion of the right leg are not detected.

Lumbar puncture.—March 31. The spinal fluid is slightly cloudy and under increased pressure. Cell count, 740 per cu. mm. A stained smear shows that the majority of these cells are lymphocytes, but a few polymorphonuclear and epithelial cells are observed. The globulin is greatly increased, and the Wassermann test is strongly positive. Serum Wassermann, positive. (Dr. Cameron.)

A clinical diagnosis of syphilitic meningitis with bilateral involvement of the trigeminal nerve, and syphilitic peroneal neuritis was made.

Treatment and Subsequent Course.—April 3. Salvarsan, 0.4 gm., was administered intravenously. The reaction was moderate.

April 5. The headache is less intense and the patient is generally more comfortable. There is no involvement of other cranial nerves, and the neurological examination is the same as at the first visit. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25) administered intradurally. An examination of the spinal fluid at the time of administration is as follows: Fluid, slightly cloudy; pressure 220 mm.; cell count, 510 lymphocytes; globulin increased; a Wassermann test was not made. Reaction to the treatment was moderate. The temperature did not rise above 99.6° F., there was some pain in the legs for 24 hours, but no nausea or vomiting.

April 10. General condition much improved. The headache and pain in the face almost entirely absent. Salvarsan, 0.6 gm., administered intravenously. Reaction moderate.

April 12. General condition improved. No involvement of other cranial nerves. Neurological symptoms unchanged. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25), administered intradurally. Spinal fluid examination: Fluid clear; pressure 220 mm.; cell count 165; globulin increased; Wassermann, not made. Reaction similar to that following the first treatment, except that the temperature rose to 101.4° F.

April 17. Salvarsan, 0.6 gm., administered intravenously. Reaction moderate. The patient was discharged from the hospital two days later, with instructions for stimulating, electrically, the paralyzed muscles, and the request to return at intervals for further treatment. Examination at this time shows that the neurological condition is unchanged. The headache and pain in the face have entirely disappeared, but there is still complete sensory and motor paralysis of both fifth nerves and right foot-drop.

April 20. Admitted to the Church Home and Infirmary for further treatment. Examination to-day shows a very slight return of sensation in each mandibular and lingual division of the trigeminal nerves, but the entire area supplied by the two upper branches of each fifth nerve is still completely anæsthetic. Mercurialized serum (Hydrarg. bichlorid. gr. 1/25), administered intradurally. Spinal fluid examination: Fluid clear; pressure 190 mm.; cell count 70; globulin, trace; Wassermann test, not made. The treatment was followed by a rise of temperature to 101° F., intense pain in the legs and slight headache.

April 21. The corneal reflex in each eye is absent, but the patient says he can feel the cotton when it is drawn across the cornea.

April 26 and May 3. Salvarsan, 0.6 gm., administered intravenously.

May 4. Examination to-day shows that there is still complete insensibility in the ophthalmic division of each trigeminal nerve, and the corneal reflex is absent in each eye; but there is a slight return of sensation in the maxillary and mandibular distribution upon both sides, although portions of these areas are still comparatively anæsthetic. The lower jaw can now be moved so that approximation of the teeth is possible. Because of the marked reaction following the previous intradural treatment, and the definite improvement in symptoms, it seems advisable to discontinue radical treatment for a while, and mercurial inunctions are ordered.

May 26. The patient's general condition shows marked improvement, and he states that he can now feel drafts of air upon the face, or in the nostrils when respired, and that he knows when he has his hat on. There is still pronounced weakness of the muscles of mastication, and objects cannot be held between the teeth, although the upper and lower jaws can be approximated. Bilateral corneal anæsthesia persists, and sensibility in the distribution of both maxillary and supraorbital nerves is still greatly impaired; but in each mandibular area sensation is practically normal. The right foot-drop is still present.

May 28. Lumbar puncture and intradural administration of mercurialized serum (Hydrarg. bichlorid. gr. 1/25). To these he reacted only slightly. Spinal fluid examination at this time: Fluid clear; pressure 240; cell count 8; globulin, faint trace; Wassermann negative; serum Wassermann negative.

The following day the patient was discharged from the hospital, and it became necessary for him to leave Baltimore two weeks later, without having received further treatment except the continuation of mercurial inunctions. In the course of eight weeks, then, five doses of salvarsan intravenously, alternating with four doses of mercurialized serum intradurally, were administered at the intervals recorded in the hospital notes.

A letter from the patient dated November 26, 1915, states: "My health has been splendid. My foot is normal again and my jaws allow me to eat everything now. The left side, which as you know, was hit hardest, is still without the fleshy muscle. My eyes, nose and upper lip are still very numb."



FIG. 1.—Photograph of the patient, April 5, 1915, showing complete jaw-drop from bilateral fifth nerve paralysis.



FIG. 2.—Photograph of the patient, April 5, 1915, showing his ability to perform ordinary facial movements. The lips cannot be closed completely because of immobility of the lower jaw.

Complete motor and sensory paralysis of both fifth nerves, without implication of other cranial nerves has, I believe, not been previously recorded in medical literature. It is true Hutchinson, Leudet, and Uhthoff have reported instances in which both nerves were involved, but an analysis of their cases shows that the affection was quite different from that which I have just described.

In Hutchinson's cases, the two nerves were not simultaneously affected, and he does not state to what extent they were involved, or whether there was implication of other cranial nerves. Leudet's¹⁰ patient, when first examined, showed disturbance of vision, ptosis, strabismus in the left eye, muscular disorders of the right eye, and anæsthesia in the entire distribution of the left trigeminal nerve. He was seen at intervals during a period of four years, after which, at the final observation, it was noted that the condition upon the left side of the face had remained practically unchanged; that, in addition, the right eye was totally blind and the entire right side of the face was anæsthetic. No note was made upon the condition of the motor portion of either fifth nerve. An autopsy was secured and it was found that the left Gasserian ganglion, which was pale, contracted, and reduced in size, had been invaded by an exostosis of the temporal bone.

Seventeen years later Labarrière¹¹ refers to a case of syphilitic involvement of both trigeminal nerves, which, by some students of the subject, appears to be regarded as an additional instance of the affection, but the case in question, No. 13 in Labarrière's studies, is identical with one described by Leudet, to whom full credit is given in the author's thesis.

Although it is impossible, without anatomical evidence, to determine the exact character and location of the lesion in my case, the syphilitic nature of the affection is evident. Hæmorrhage into, or acute inflammation of both trigeminal nuclei would, of course, produce bilateral fifth nerve paralysis; but the subacute onset of the disease does not suggest hæmorrhage, and it is improbable that a pontile lesion of this extent could occur without neighborhood symptoms, or even a fatal termination.

That intense meningitis was present is indicated by the unusually high cell count in the spinal fluid; but it is unusual to witness this degree of meningitis without implication of other cranial nerves. Bilateral syphilitic ganglionitis suggests a probable explanation, but such a condition, if confined within the dural covering of the ganglia, makes it difficult to explain the marked lymphocytosis in the spinal fluid. Diffuse meningeal inflammation upon the surface of the pons might involve the trigeminal roots upon each side, and account for the cytological changes in the spinal fluid. It is not probable, however, that the sixth nerves would have escaped in such a lesion. Local meningitis upon each lateral aspect of the pons, but not extending across the mid-line, might produce bilateral trigeminal radiculitis and resulting paralysis of both nerves without implicating the sixth nerve, or those lateral to the fifth nerve. Such a lesion would account for the lymphocytosis and at the same time explain the long duration, and perhaps

permanency of some of the symptoms, from central degeneration of the sensory fibers. While it may be difficult to locate, exactly, the lesion in this case, there is little doubt that the symptoms were due to intracranial involvement of both fifth nerves.

There are two important clinical features which deserve especial emphasis. Trophic disorders following lesions of sensory ganglia are not infrequently observed, and it is not improbable that the bilateral auricular eczema may have been of this origin. In Neiding's case, furunculosis of the nasal cavity upon the affected side was attributed to the same cause.

According to Nonne, Rumpf has been unable to find in the literature a single instance of syphilitic disease of the fifth nerve in which taste was lost. This statement is, however, contradicted by Neiding, in whose patient taste was lost upon the anterior two-thirds of the affected half of the tongue. In view of Rumpf's studies and the preservation of taste in the case which I have studied, it appears that the centripetal fibers conducting this special sense do not enter the central nervous system by way of the Gasserian ganglion. It is not improbable that the loss of taste in Neiding's case may be explained by an extension of the inflammatory process into the trunk of the mandibular nerve with involvement of the incorporated fibers of the chorda tympani.

It is a pleasure to acknowledge my indebtedness to Dr. Hugh H. Young for referring the patient to me, and for the privilege of conducting this study in the Brady Urological Institute.

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DIGESTION: AN HISTORICAL SURVEY.

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Any survey of the views that have been held by mankind in the past on the subject of animal digestion and bodily nutrition must necessarily be synchronous with the history of medical science.

The majority of ancient medical records that have come down to us are largely occupied with references to diet and descriptions of imaginary causes of ill-health. In the absence of direct testimony as to the conception held by the ancients with regard to the manner in which the food they ate nourished their bodies, we are forced to rely upon statements throwing a side-light on the general subject.

The ancient Egyptians held the belief that food was the chief source of disease, and they followed precept by practice in taking a purgative and an emetic three times a month. However, there was also present in the Egyptian mind the idea that the body was ruled by demons, and that digestion was performed by the aid of a "demon" or spirit, whereas indigestion was due to the anger of the spirit.

The authors¹ of the great epic poems of the Hindus have given evidence, however, of the existence of other theories related to demonology, according to which principles or humors were supposed to reside in the body and to direct the natural digestive processes. Thus the Aryan writers recognized three principle humors: *Vata*—situated between the feet and the navel—or Wind; *Pitta*—between the navel and the heart—or Bile; *Kafa*—between the heart and the top of the head—or Phlegm.

Kafa was predominant during the period when the food was in the mouth; *Pitta*, during the course of digestion; and *Vata*, after the food in the stomach was fully digested. If from any cause any one of these principles became unduly prominent, the condition of the bowels was affected. Thus, when *Vata* exercised too strong an influence, the bowels were costive; when *Pitta*, or the bile, was in the ascendant, they were loose; whereas they acted normally when *Kafa* was the most powerful.

These writers also describe a *Pachaka*, or fire of digestion, situated between the stomach and the small intestine, which assisted digestion and imparted heat to the body. *Pachaka* was also able to separate the nourishing portions of the food from the dejecta.²

Among the Chinese the medicine and physiology of yesterday are the same as that of to-day. They and their civilization, like mountains, have attained a certain limited height, have existed there, inflexible and almost unchanged, for thousands of years. Physiology occupies the lowest grade in Chinese medical science and nothing of value or interest relating to the subject of digestion is to be found in their medical literature.

Among the ancient Chaldeans, Babylonians and Persians we find that medicine probably presented the lowest form that has ever existed in civilized communities. The Chaldeans appear to have contributed absolutely nothing to the general stock of medical knowledge.

The medicine of the Medes and Persians resembled somewhat that of the Chaldeans, but had a still closer analogy to that of the Hindus, with the important difference that it produced no *Susruta* or *Charaka*.

Turning our attention to early Greece, we find that their philosophy exercised so essential an influence upon their medicine that the fundamental doctrines of the former formed the theoretical principles of the latter, and we cannot well keep the two separate. In fact, the whole medicine of the Greeks bears the special character of a philosophical science, if we except that of Hippocrates alone.

Nevertheless, from quite an early period, the medical writers of the ancients recognized that the stomach was one of the chief organs concerned in digestion and they paid considerable attention to it. According to these Grecian natural philosophers, the food, after it was taken into the stomach, putrified or was cooked. Anaxagoras (500-428 B. C.), a member of the Ionic school (600 B. C.) and teacher of Pericles, imagined that the animal body, by means of a kind of affinity, appropriated to itself from the nutritive supply the portion similar to itself. His philosophical influence was great, but a more important influence, especially later, was exercised by Empedocles (504-443 B. C.), whose assumption of the four elements—water, air, fire, and earth—formed a foundation stone for the doctrines of Hippocrates II of Cos, justly named the Father of Medicine.

It is not within the province of this paper to extol or to magnify the achievements or failures of medical celebrities, except in so far as they may be related to the historical development of our knowledge of digestion. Hippocrates taught that gastric digestion was brought about by a sort of internal cooking or coction—"pepsis" (digestion)—possibly through the agency of the "innate heat"³ of the body. The views of the Hippocratists were based upon the assumption of the four elements of Empedocles—fire, water, earth and air—whose mixture and cardinal properties (warmth or heat, coldness, moisture and dryness) formed the body with its constituents. To these corresponded the cardinal fluids, blood, phlegm, black and yellow bile, in the order mentioned. The heat or warmth from the blood caused digestion of food. The liver formed blood and bile and assisted the process of coction in the stomach by increasing its heat. To certain foods were ascribed qualities corresponding to the four humors, and such foods were recommended for maladies due to excess or defect of the humors. Thus to Hippocrates and his followers we owe the

¹ See Jee: History of Aryan Medical Science, London, 1896.

² By some this body was looked upon as being identical with *Pitta*, or bile. The author of the "*Rasa-pradipa*" imagined it to be a minute heating substance situated in the centre of the navel.

³ *Callidum innatum*, the "animal heat" of later physiologists. (See Harvey.)

foundation of a science of dietetics. But about their ideas on the physiology of digestion nothing further need be said.

Next there appeared the philosophy of Plato (427-347 B. C.), which, paying slight respect to all facts and holding all observation by the senses as deceptive, won a controlling influence over medicine. Plato, though the noblest of philosophers, has hardly deserved well of the profession of medicine. As so often happens, the enunciation of a rational doctrine by Hippocrates tended to cause a reaction, and men now began to seek to deduce the underlying principles of physiology and disease, not from the study of facts, nor from the evidence of the senses, but from purely mental speculations. Reflection ranked higher than experience. The hold which this method of solving physiological problems obtained on the physicians and thinkers of that time retarded the advance of physiological knowledge by a period only to be reckoned by centuries. Plato, for instance, gravely propounded the theory that some of the fluid drunk passed through the wind-pipe into the lungs, and there served to cool the heart; the liver served the lower desires; the spleen furnished an abode for the impurities of the blood. The intestine was long and tortuous, in order that the food need not be renewed so often and thus disturb the contemplations of the mind.

Aristotle (384-321 B. C.), the teacher of Alexander the Great, exercised no such important and immediate influence upon the views of ancient medicine as did Plato. He did not, like Plato, call about him a numerous school of followers; nevertheless, his great mind supplied for centuries the principles of thought and observation, and the material for the extension of all branches of knowledge, but especially of the natural sciences, of which he is considered the creator. He did much to break down the excessive idealism current in the system of Plato, and to bring thought back into more realistic grooves. Like the Father of Medicine, he looked upon digestion as brought about by a process of coction in the stomach, the resulting chyle proceeding to the heart. He looked upon the blood as the medium by which the nutritive material for the growth and warming of the body was conveyed through the vessels. Bile he regarded as a useless excrementitious product.

The school of Alexandria, founded by Herophilus and Erasistratus (about 330-280 B. C.) covered a period, which when compared with the preceding dogmatic tendency of medicine, must be regarded as an epoch of realism.* It was distinguished by the appearance of the famous founder of human anatomy, Herophilus of Chalcedon, and of Erasistratus of Inlis, a physician valued no less highly than his contemporary. They, however, differed widely in their tenets.

Herophilus possibly discovered the chyloferous and lymphatic vessels, and the duodenum, which he named; he also described the liver quite accurately. He was a follower of Hippocrates and of the humoral doctrine. Erasistratus, however, discarded the humoral system, and propounded one of his own, based upon the theory that the arterial vessels and heart contained "vital

spirits" (pneumata). He ascribed digestion to the result of trituration of the food between the stomach walls (Iatro-physician!), nutrition to the addition of new particles, and secretion to the action of what he termed the non-attractive force. He thought that the bile was useless, the spleen superfluous, and showed that fluids did not enter the air passages.

Few records have come down to us of the medical opinions current among the inhabitants of early Rome, but in so far as we can speak of such an art, it did not rise above the very first rudiments. Gradually with the advent of Grecian medical influence some advancement was made.

At a much later time (200-131 A. D.) flourished the most famous of all the Roman physicians, Claudius Galen, of Pergamus. He was a man who not only knew all there was to know in his age, but who also possessed sufficient talent and originality to acquire the position of a medical dictator, and to maintain it for more than a thousand years. His physiology, though somewhat marred by excessive theorizing, was admirable. Following Hippocrates and the Alexandrians, he emphasized the great importance of the study of anatomy and physiology, and performed many experiments in both of these sciences.

Galen believed that the food, after it reached the stomach, was digested by the process of "coction"; the results of digestion were then carried to the liver by the portal vein, where they were transformed into blood (an important error which was not discarded until the 17th Century). This blood, now called "natural spirits," was then carried to the heart where by the aid of the innate heat of this organ, it was laden with "vital spirits." The heart then drove into the lungs, through the pulmonary artery, as much of the blood as was required for their nutrition. At the same time the remainder of the blood was driven through the veins to all parts of the body, supplying its various portions with nutriment. Galen, therefore, considered the venous portion of the circulation as the seat of nutrition. The arterial blood (blood laden with vital spirits), upon reaching the brain, there generated the "animal spirits."

Little of interest or of value can be gathered from the writings of those who followed Galen. For a period to be measured only by centuries the current opinions were only variants of Galen's views. In the dark ages of Medieval Europe the tendency of all knowledge was to recede rather than to advance; indeed, the influence of Christianity tended to hasten the decline of medicine instead of advancing its progress.

The standard of Arabic medicine, it is true, was at its highest development from the 8th to the 10th Century, but it offers us little or nothing in the way of advancement in physiological knowledge.

Early in the history of the Middle Ages, we find medicine and religion more or less firmly united together, and, from the 6th Century onward, everything medical gradually fell into the hands of the Church, and especially of the monks, whose ignorance of medical science is only too well known to medical historians. The authority of the Church in all branches of knowledge soon became paramount, and for many centuries it controlled more or less absolutely the gates of learning. The search for truth ceased to be the study of natural phenomena

* Called by Baas, without much error—"The epoch of antique scientific, or exact, medicine."

and the search for the reason why: it narrowed itself down to asking, "What does the Church say about it?" Truth and science came to mean simply that which was written, and inquiry became mere interpretation.

However, with the dawn of the Renaissance, the various medical sciences—atomy, physiology and chemistry—again began to develop and the writings and teachings of such men as Vesalius (1514-1564), Servetus (1509-1553), Paracelsus (1493-1541), and Borelli (1608-1679), were in part the instruments which served to shatter to pieces the idol of authority, which was never to be put together again.

Vesalius contributed little or nothing, directly, to the science of physiology, but by his anatomical dissections he paved the way for many future physiological discoveries; and in truth we may look upon him not only as the founder of modern anatomy, but also as the distant forerunner of the English physiologist, William Harvey (1578-1661), whose discovery of the circulation of the blood opened up the avenues for scientific physiological and chemical research which has given so many glorious discoveries to the world.

Paracelsus exerted a great influence upon the development of medicine, especially chemical physiology, through his teachings in mystic alchemy, so that by some historians he is called the founder of chemical physiology.

Borelli, likewise, by his numerous experiments and discoveries in the new and infant science of physics, of which he was the real founder, hastened the development of physiological knowledge.

The 11th Century saw the birth of two distinct sciences—physics and chemistry—the latter emerging from a mystic alchemy. It was not long before they were pressed into the science of physiology, sometimes unwisely, whereby the school of physiology proper was split up into the school of those who would explain all the phenomena of the body on physical and mathematical principles, the *iatro-mathematical* or *iatro-physical* school, and into the school of those who proposed to explain all the same phenomena as mere chemical events, the *iatro-chemical* school.

In the study of the historical development of our knowledge of digestion, it is necessary to inquire into the manner in which chemistry came to the aid of those who were studying the problems of life, and thus gave rise to the chemical physiology which we know to-day.

Among the medical celebrities whose influence in the advancement of chemical physiology was paramount, the names of the chemical mystics, Basil Valentine (1450-?),⁶ Paracelsus or Theophrastus Bombast von Hohenheim,⁷ and van Helmont must be considered first of all.

According to historians, Basil Valentine was probably a Benedictine monk living at Erfurt about the middle of the 15th Century. He was one of the alchemists and apparently the author of certain conceptions which played an important part in the development of chemistry and physiology.

⁶ Paracelsus, born at the close of the 15th Century in Maria Einsiedeln, Switzerland, was the son of a physician and, at the age of sixteen, is said to have entered the University of Basel and

Basil Valentine is generally credited with the conception of the three "elements," replacing the old idea of the ancients of the four elements—earth, air, fire and water. He designated these three elements, sulphur, that which is combustible; mercury, that which is volatile; and salt, that which remains after burning. To this conception of the properties of matter he added his *archæus*, or *archæi*, which were to him the spiritual forces governing and determining the phenomena of the universe, chemical changes included.

Apparently the doctrines of Basil Valentine obtained a firm hold upon the mind of Paracelsus. He greatly enlarged and developed them by the new light he had gained by his own researches, observations and studies. He was a chemist through and through, but delighted to enshroud his chemical conceptions with the veil of mysticism.

According to him, the two important facts of Nature were visible matter and invisible forces. The former consisted of the three elements—sulphur, mercury and salt, with their properties, which were capable of bringing about changes in this visible matter. The latter were spiritual forces, prominent among which were the *archæi*, to which matter was subject and by which its changes were governed. All chemical and physiological processes were governed by the *archæus*. He looked upon digestion as carried out by this presiding force or spirit within the body. Its home was in the stomach and it separated the material useful for nutrition, the "essence," from the useless, the "poison," and thus became the alchemist of the body. Digestion was to him a kind of putrefaction, by which, on the one hand, the assimilation of the nutritive slime, on the other, the formation of the excrement, was rendered possible. Health was recognized by the regular action of this *archæus*; disease, i. e. indigestion, was the failure of the *archæus* to govern aright.

Such conceptions as these were considered by Vesalius and his followers as the ravings of an ignorant charlatan. Nevertheless, after a lapse of nearly one hundred years they were taken up by a man, who so handled them that, in a modified and developed shape, they found lodgment in ordinary medical teachings and served as the starting point of that chemical investigation of the problems of living beings, which since that time, and especially in these later years, has been so fruitful of results. As Paracelsus, with the aid of some fifty years of increased knowledge, extended and developed Valentine's ideas, so his doctrines were in turn extended and developed with the aid of one hundred years of increased knowledge by van Helmont.

Jean Baptiste van Helmont⁸ (1577-1644) is almost as strik-

soon afterwards to have studied under Bishop Trithemius at Würzburg. Later he traveled extensively and finally settled at Bâle, as a physician, in 1527. Regarding his personal history, however, there is much uncertainty. Many of his writings, discoveries, theories, and even his language, in places, are so exact reproductions of Basil Valentine's, that it is not difficult to presume that he had seen his predecessor's works in manuscript and made extensive use of them. There is also the probability that he was taught his doctrines while a pupil of Bishop Trithemius.

⁷ Born at Brussels in 1577, some thirty-six years after Paracelsus' death and thirteen years after that of Vesalius.

ing a figure in medical history as Paracelsus, whom he resembled in many respects, though he surpassed him both in genius and also in learning.

In studying the writings and character of van Helmont we seem to be brought face to face with a dual personality—with two intellects of quite different kinds. There is the patient, careful and exact observer, a child of the new learning, who takes advantage of all the new discoveries and teachings; but beneath it all we can see the mystic, speculative dreamer and philosopher, weaving a fantastic scheme of the powers and forces ruling the universe, and calling in the aid of invisible supernatural agencies to explain the occurrence of natural phenomena. Throughout all his writings may be seen the continued endeavor to weave his exact chemical and physical knowledge and his spiritualistic views into a consistent whole.

Van Helmont's conceptions may be regarded as a peculiar remodeling of the pantheism of Paracelsus into a mystic and pietistic system, based upon more or less exact chemical principles. Throughout his writing we find the use of two new terms, "Blas" and "Gas." By the former he meant in all probability the *archæus* of Paracelsus; by the latter he clearly disentangles himself from all the mystic Paracelsian lore and earns for himself the title of the first of modern chemists, and at the same time the first of chemical physiologists. By "Gas" he probably meant, what we now call carbonic acid gas or carbon dioxide. "Gas" he observed to be formed in various fermentative processes by the action of a ferment, as in the making of wine or bread. He was deeply impressed with the idea of the action of ferments and makes it the basis of his system of physiology. Digestion, as well as all other changes in the body, was looked upon as a process of fermentation. And he reconciled this view with his acknowledgment of the influence of the "Blas" or *archæus* by putting forth the hypothesis that these spiritual agents worked, not by acting directly on matter, but by making use of the ferments, which were thus their servants or instruments.

The current teachings of the day regarding digestion and nutrition were in substance those of Galen. The food absorbed from the stomach and intestine was imbued with natural spirits in the liver; in the heart the natural spirits were converted into vital spirits; and in the brain the vital spirits were converted into animal spirits.

According to van Helmont this teaching was entirely wrong: instead of three there were six conversions or digestions, by which the food was transformed into the living body tissue.

To him the whole body was under the influence of an *archæus influus* or vital principle, which resided in the stomach, while every organ had its own individual *archæus insitus* directing the processes natural to it. During the process of digestion in the stomach, his so-called *first digestion*, the local *archæus* generated a ferment whereby an acid was produced to dissolve the food. This ferment, he believed, had its origin in the spleen and it was from this organ that the stomach drew all its energy. The ferment was an acid ferment, *fermentum acidum*, but the acidity was not the ferment itself, it was only the organ or instrument of the ferment.

The food, as acid chyle, then passed into the duodenum where it at once acquired a saline nature—it was the change of an acid into a salt. This duodenal change constituted his *second digestion* and was affected by a ferment furnished by the bile.*

The *third digestion* was that of sanguification, taking place in the mesenteric veins, liver and vena cava, and consisted in the conversion of the chyle into crude blood, brought about by the aid of another hepatic ferment.†

We might, with much truth, compare these three digestions with what even now-a-days we sometimes call primary and secondary digestion.

It is difficult to differentiate clearly between his *fourth* and *fifth digestion*, the former consisting primarily in the conversion in the heart of venous into arterial blood, while the latter "changes the blood of the arteries into the vital spirit of the *archæus*."

The *sixth* and last digestion took place in the kitchens of the several members, for there were as many stomachs as there were nutritive members. In this sixth digestion a spiritus, a ferment innate in each place, cooked its food for itself. "A vein," says van Helmont, meaning probably an artery, "may be considered as a vessel containing aliment prepared for the kitchens of the tissues, but it is not their kitchen. Each tissue maintains its own individual kitchen within itself." In other words, all the tissues live upon the common blood, and the power of assimilation lies in the tissue itself; it is the tissue and not the blood which primarily determines assimilation, the qualities of the blood have only an indirect influence.

Van Helmont's exposition of the mechanism of the digestive process exerted a great influence on investigators who followed him. It showed that many of the problems of the living body were chemical problems to be solved by chemical knowledge, and also a large number of the processes taking place in the living body were more or less akin to the process by which yeast produces alcohol, as in wine-making, and therefore may be spoken of as fermentations. The idea of fermentations had long been known, but its definite introduction into physiological thought is due to van Helmont.

Francois De le Boe (or Dubois), better known as Franciscus Sylvius,‡ was one of the direct successors of van Helmont in the field of chemical physiology. He was the foremost and most typical representative of the iatro-chemical school.

Van Helmont was but little influenced by the new discoveries in physiology, chemistry, anatomy and physics, whereas Sylvius was well versed in all these matters. In contrast to van Helmont, he would have nothing to do with mystic speculation about invisible agencies and spirits. He followed van Helmont, however, in considering many of the changes

* Van Helmont knew nothing of pancreatic digestion. Wirsung had not yet made his discovery of the pancreatic duct (1643).

† No mention of the lacteals is made, although he certainly must have been cognizant of Aselli's discovery in 1622.

‡ Born in Hanover in 1614; died at Leyden in 1672. He became professor of Medicine at Leyden in 1658 and for twelve years exerted a most powerful influence by his teaching.

within the body as being of the nature of fermentative processes; but to him, this fermentation was a true chemical change—an “effervescence,” and he saw no reason for any additional intervention of subtle agencies, as did van Helmont.

The 17th Century was rich in new discoveries, with many of which Sylvius was by no means unacquainted. You may recall that Aselli discovered the lacteals in 1622; Harvey, the circulation of the blood in 1628; Wharton, the submaxillary duct in 1655; Stenson, the parotid duct in 1661; Wirsung, the pancreatic duct in 1642; he also appears to have observed the pancreatic juice. De Graaf made investigations on the pancreatic juice in 1664, as well as on saliva and bile. Jean Pecquet, in 1651, made known his discovery of the receptacle of the chyle and its continuation as the thoracic duct and traced it into the venous system at the junction of the jugular and subclavian veins. Two years later, 1653, Rudbeck, of the University of Upsala, described the vessels which we now call lymphatics. He saw them first in the liver and intestines and traced them to the thoracic duct, of whose existence, he says, he had become aware in 1650, before the publication of Pecquet's book. In 1673, one year after Sylvius' death, Peyer published a little tract, in which he described certain new glands of the intestines, now known as Peyer's patches. And finally, in 1682, Brunner succeeded several times in removing from a dog nearly the whole of the pancreas, and in keeping the dog alive afterwards for a considerable time. Five years later he described the glands in the duodenum, since known by his name.

Van Helmont knew nothing of either salivary or pancreatic ducts, but Sylvius with this added knowledge was led to attach the greatest possible importance to saliva; in fact, it was to him a type of the fermentative juices, and he attributed many of the changes taking place in the stomach to the saliva swallowed with the food rather than to the ferment provided by the stomach itself. The first stage of the fermentation, called chylication, was brought about chiefly through the action of this salivary secretion, according to Sylvius' view; the second stage of digestion was due to the interaction of the bile and pancreatic juice. De Graaf, his eminent pupil, had convinced himself that the pancreatic juice was of an acid nature, and this supposed truth became a foundation stone of Sylvius' views on digestion. Apparently, led away by a preconceived theory, he failed to recognize the alkalinity of the pancreatic juice and persistently insisted that it was acid, believing its use in digestion was to effervesce, to ferment, with the bile. But neither Sylvius nor his pupil seemed able to clearly explain just how it promoted digestion. De Graaf tells us that the “effervescence attenuates the viscid mucus lining the interior of the intestine, the presence of which might hinder the absorption of chyle by the lacteals; while it also assists the separation of the useful parts of the food from the useless”; but there is no explanation given how this is brought about.

According to Sylvius, in the next stage of digestion, the chyle, or the nutritious part of the food, passed into the lacteals and was conveyed through the thoracic duct into the venous system. The blood carried to the right heart by the upper great veins was chylous blood. In the right side of the heart it

met with the blood of the vena cava, which he termed bilious blood, because he believed that the bile was secreted by the gall-bladder and that that part of it which was not needed in digestion was carried by the cystic duct back to the liver, where it passed into the venous system, whence, mixed with the blood, it was carried by the vena cava to the heart.

Glisson (1597-1677) and later Malpighi (1628-1694) disproved this erroneous view, but it greatly aided Sylvius in the explanation of his views of digestion and he clung to it tenaciously. According to him, the “chyle assumes the form of blood (a superficial initial change) owing to the bilious blood ascending to the heart, meeting in the right auricle and especially in the right ventricle with the lymphatic blood (of the superior vena cava) with which the chyle is mixed, and so, on account of the different or rather opposite disposition of each (kind of blood), in certain of their parts provoking an effervescence of great moment.” But the “chyle reaches the ultimate perfection of blood through the continued and tempered effervescence, which by reason of the breathing of air takes place in the lungs, in the left auricle and ventricle of the heart and in the large trunks of the aorta. By the energy and help of this effervescence we think that there bursts out and springs forth the vital fire, which by rarefying the more fatty and oily parts, not only of the chyle added to the blood, but of the blood itself, and by loosely uniting together at the same time all other parts, reduces the whole into a heterogeneous, homogeneous mass and so converts the chyle into true blood.”

His exposition is vague indeed, but beneath it all we can recognize his efforts to explain, in the light of added chemical knowledge, that it is unnecessary to take refuge in subtle influences and occult agencies; that all changes taking place within the body are more or less purely chemical in their nature and can readily be reproduced by experiment in the chemical laboratory.

We must at least give to Sylvius the credit of showing that there was no connection between chemistry and spiritualism; that, on the contrary, the newer chemistry in its attempt to solve vital problems was treading the path of the most naked materialism. In all probability, it was to this opening up of a line of inquiry into chemical physiology free from any taint of mysticism, that the great influence, which as a teacher he undoubtedly exercised, was largely due.

In contrast to the iatro-chemical school of which we have been speaking, there was developing during this period the so-called iatro-mathematical or mechanical school of which Giovanni Alphonso Borelli (1608-1679) of Naples was the founder, with such followers as Redi (1626-1697), the sagacious naturalist, Archibald Pitcairn (1652-1713), the British representative of the school, Lorenzo Bellini (1643-1704) of Florence, and Giorgio Baglivi (1668-1707), a pupil of Malpighi.

This school based the phenomena of digestion and other physiological processes upon the action of mechanical laws. After the manner of Erasistratus the whole process of digestion was referred to trituration by the interaction of the stomach walls.

Borelli had pointed out the great grinding, crushing force which was provided for by the muscular coats of the stomach of birds, and thought he had proved his point by feeding turkeys glass globules, hollow leaden tubes, etc., and the next day finding the leaden masses crushed and eroded and the glass pulverized. He admits that birds of prey and fishes, which are destitute of teeth and possess a membranous stomach rather than a muscular one, digest hard food in a different manner. "These animals consume flesh and bones by means of a certain very potent ferment much in the same way as corrosive liquids corrode and dissolve metals. Such a corrosive juice is poured forth by the small glands with which the membranous substance of the stomach is crowded."¹¹

Archibald Pitcairn (1652-1713) like the English school generally, was far more exclusively mechanical than the Italians, and would have nothing of acids or ferments even in digestion. "That the stomach is fully able to comminute the food may be proved by the following calculation," says Pitcairn. "Borelli estimates the power of the flexors of the thumb at 3720 pounds, their average weight being 122 grains. Now, the average weight of the stomach is 8 ounces, therefore, it can develop a force of 117,088 pounds, and this may be further assisted by the diaphragm and abdominal muscles, the power of which, estimated in the same way, equals 461,219 pounds." Well might Pitcairn add that this force is not inferior to that of any millstone!

The futility, indeed, of this mode of viewing the subject, is signally illustrated by the fact, that, whereas Pitcairn had allotted to the stomach fibres such an enormous power, Borelli thought that 1350 pounds was more correct. Hales believed that 20 pounds would come nearer the truth, and Astruc valued its compressive force at 5 ounces.

It was many years, in fact the greater part of a century, before further contributions were made to the knowledge of the subject of digestion. It is true that at the close of the 17th Century and the beginning of the 18th Century, there flourished two men who achieved great eminence as chemists and who were assiduous in applying their chemical knowledge to physiology; but, so far as digestion is concerned, their influence was rather that of expositors than that of discoverers. I refer to George Ernest Stahl, born in 1660 at Anspach, and Hermann Boerhaave, born near Leyden in 1668.

Stahl, employing the term Animism, ascribed the force used in digestion, as well as in all the chemical changes taking place in the living body, to the "sensitive soul." His conception had not a little kinship to van Helmont's; indeed, his views may to a certain extent be regarded as a development of it. The sensitive soul of Stahl is that of van Helmont with two differences only. It works directly on chemical processes, without the intervention of *archæi*, and is not a mortal something

associated with, and as it were the shell of, an immortal mind, but it is itself the immortal principle, spiritual and immaterial, coming from afar, and at the death of the body returning whence it came.

Speaking of the physiology of digestion, Stahl seems to admit fermentation as a property of non-living things and to regard putrefaction also as a sort of fermentation, possible in and belonging to non-living things. Apparently, he regards the ferments of saliva and pancreatic juice as non-living agencies, although he refuses to believe in a gastric ferment.

Boerhaave (1668-1738), the teacher of Haller, was a man of wholly different mind and, although a learned scholar and a sound scientific thinker, he cannot be said to have made any striking contribution to our knowledge of digestion. Essentially eclectic in nature he combined in his conceptions of physiological processes many of the doctrines of earlier systems.

He recognized that digestion was, in part at least, a solution of some of the constituents of the food by means of various juices. Saliva, the juice from the esophagus, the gastric fluid, which consists in part of a viscous secretion poured out by the glands of the stomach, and in part of a thin fluid secreted by the arteries, the bile, the pancreatic juice, and the intestinal juice, each of these contributed to the result. But he regarded the solution effected by means of these juices as of the nature of an ordinary solution, and not of a fermentation. He denied the acidity of the gastric juice. In common with his contemporaries, Boerhaave regarded the nerve supply to the stomach as out of all proportion to the movements or sensations of that organ and believed that a nervous fluid, having some share in the digestion of food, was poured into the cavity of the stomach from the endings of the nerves.

He joined with the mechanical school in believing that the more fluid and nutritious parts of various articles of food were expressed from them by trituration in the stomach. In particular he thought that bones were not digested, only crushed. He was more or less antagonistic to the doctrines of fermentation, and regarded the action of the juices as a mere solution, not as a proper fermentation. Nevertheless, he held that solution and trituration are, in digestion, aided by something else. He thinks that the stomach contents, being exposed to considerable heat, undergo "an incipient fermentation by means of which the chyle is impressed with the primary principle of vitality."

These doctrines of Boerhaave became the dominant ones for many years: indeed they were taught by his illustrious pupil, Haller, nearly fifty years later.

Albert von Haller was born at Bern in 1708 and in 1725 went to Leyden to work under the renowned Boerhaave, where he undoubtedly laid the foundation of all his future work. Haller was a universal and indefatigable savant, of ingenious natural endowments, a marvelous, almost unique, capacity for work, absolutely conscientious, a man of inextinguishable love for science and art, and one of the greatest medical thinkers of all times, as well as a notable poet, botanist and statesman.

¹¹ Regarding the presence of this corrosive juice in the stomach and its influence upon digestion, we find that the followers of Borelli went beyond their master and were prepared to deny chemical action in all cases and to maintain that digestion was in reality a mere trituration of the food by the muscular mill of the stomach into the creamy mass known as chyle.

In 1755 he began to publish his "*Elementa Physiologica*," the eighth and last volume leaving the press in 1765. This great work may be taken as a trustworthy account of the knowledge of the time with regard to the questions therein stated.

In his exposition of digestion he considered the saliva to be neither acid nor alkaline and regarded its use as being that of softening the food and helping deglutition. He recognized the importance of the tunica villosa of the stomach, but says that the glands therein contained furnished the mucus of the stomach only, the true gastric juice, the *succus gastricus*, being secreted by the arteries. He discarded the idea of Boerhaave that a nervous fluid, oozing from the endings of the nerves, intervened in gastric digestion. He believed that pure gastric juice was neither acid nor alkaline, and while speaking of it as a macerating liquor which softens and dissolves the food, he refused to regard it as a ferment. He held that it was not a corrosive liquid, like many acids, and, though at times it might be acid, the acidity was a token of the degeneration of the digested food, not of digestion itself.

He regarded trituration as a useful aid, especially where hard grains form a part of food, as in that of birds, but only an aid. "They have done well who have brought back to its proper mediocrity the power of trituration so immensely exaggerated."

He looked upon bile not as a mere excrement, as some had done before him, but as a secretion from the liver substance. It was a fluid viscid and bitter, but not acid, and indeed not alkaline, a fluid which had the power of dissolving fat. He added that the bile must have some other function than that just described; "for animals deprived of their gall-bladder very rapidly perish, the exact cause of their death not being clear."

In considering the pancreas he says, "A part at least of the usefulness of pancreatic juice will be to dilute and soften the cystic juice, so that this mixes better with the food." He adds, "There may be other functions of the liquid not as yet well known to us"—a sentence perhaps prophetic of the work of Bernard a hundred years later.

In this brief review of the opinions and theories of the eminent men of science living before the middle of the 18th Century regarding the subject of digestion, we find that to van Helmont the stomach with its acid character was the important organ of digestion; that others following him insisted that other juices were of more importance but that most of them, though they admitted a certain potency to the gastric juice, either doubted or denied its acidity. The veil of doubt was, however, soon to be lifted, and thus to reveal the true nature and function of the gastric juice.

The year 1752 is indeed a red-letter year in the history of our subject. In that year were published two treatises upon the "Digestion of Birds" by René Antoine Ferchault de Réaumur, which mark an epoch in the history of digestion by indicating the dividing line between modern ideas of physiological processes and all that had gone before. Réaumur was one of the most striking men of science of the 18th Century. Born at

Rochelle, France, in 1683, he moved to Paris at the beginning of the 18th Century. He was a wealthy man and used the opportunities thus afforded him in carrying out many and varied scientific experiments. But it is only of his work on digestion of birds that I shall now speak. In these experiments he attempted to learn whether the digestion of food was due to trituration, putrefaction, or to solution, brought about in some way by means of the gastric juice secreted by the stomach. He devised a means of determining whether the comminution and solution of food is effected by the action of the gastric muscles. This he accomplished successfully by obliging animals to swallow metallic tubes opened at both ends, save that each end was secured with a grating made of threads or fine wire, and filled with their natural food, such as grains, etc., for granivorous fowls. He argued that if these grains, after remaining in the stomach, were broken down and decomposed, we must assign a dissolving liquor as the cause of the phenomenon, since the sides of the metallic tubes must have presented an insuperable obstacle to the action of the gastric muscles upon the contents; but that if they were returned in a sound and entire state, it must be acknowledged that in these animals digestion does not depend on a solvent, but on muscular action. His first memoir deals with digestion in granivorous birds—those possessing a gizzard or muscular stomach.

A few hours after they had swallowed the grains, Réaumur killed the animals and removed the tubes for examination. He found barley grains, etc., quite entire, whence he inferred, that in these animals, the food was not broken down by a solvent, but by the strong action of the muscular stomach. He further observed that if the tubes were quite thin, they were frequently broken, crushed or distorted in a most singular manner. These results need not surprise us if we but recall the observations of Redi and Borelli, that ducks, fowls, and pigeons pulverized hollow globules of glass in a very short time."

"This hypothesis of Vallisnieri is evidently groundless," says Spallanzani, "for seeds remain unaltered whenever they are defended by tubes. As when pigeons, fowls and turkeys are forced to swallow several balls of glass at once, some in tubes and others naked, the latter are reduced to small fragments as usual, while the former remain entire. The gastric muscles are the chief cause of this effect."

It had been long known that fowls always have a supply of pebbles in the stomach. It was observed by Redi, Borelli and others, when members of the Academy of Cimento, which was established in 1657 under the patronage of Prince Leopold, that the ducks and fowls that had the greater number of stones in their stomachs more quickly reduced spheres of glass to powder. Redi thought that the stones performed the office of

"It may also be of historical interest to mention that Vallisnieri of Padua (1661-1730) stated in his anatomy of the ostrich, that the hardest substances, such as stones, wood, glass and even iron are reduced to pieces in the stomach of these enormous birds by a solvent. Moreover, he was inclined to think that glass was attacked and broken by a similar liquor, which he believed existed in the stomach of fowls, without the concurrence of muscular action."

teeth, while Réaumur believed that they were necessary to digestion.

The greatest part of Réaumur's first memoir deals with the great force of the gizzard of fowls in triturating the food; in the remainder he endeavors to prove that this viscus contains no menstruum of sufficient efficacy to produce solution. In support of this he mentions the following points based upon experiments: (1) Barley grains remained unaltered within the tubes; and (2) ducks were given small particles of meat in tubes and on removal from five to twenty-four hours later, some pieces had retained their red color (some, however, had lost it) and there was also no appreciable diminution in amount. From this he inferred that no menstruum had acted on the meat, since it was not comminuted or much dissolved, and he even concluded that the gizzard contains no solvent capable of decomposing and digesting the aliment.

In his second memoir he inquired into the nature of the function of digestion in carnivorous birds, whose stomachs are membranous in type. He chose a kite as the subject of his experiments, taking advantage of its well known habit of vomiting indigestible things which it had swallowed. He used tin tubes filled with different substances, especially meat, which were thrown up, after a certain time; and that the meat was more or less digested, according to the time it was in the stomach, was the general and invariable result observed. Hence, he justly inferred, that here digestion is produced by the gastric fluid, without the concurrence of any triturating power. From other additional experiments he also concluded that digestion in other birds with membranous stomachs is produced in a similar manner.

On several occasions he had observed that when his tubes containing flesh and grain were rejected, they were filled more or less completely with a yellowish, somewhat opalescent fluid, which to the taste was salty and bitter. Obviously it was this fluid which had dissolved the food and he asks himself these questions: "What is this liquid which acts on flesh, but has not the same power on starch? To which of the solvents which chemistry offers us can this liquid be compared?" To answer these questions he filled his tubes with small pieces of sponge, from which, when rejected, he squeezed out the fluid which they had imbibed. In this way he obtained a small amount of an opalescent fluid, salty to the taste, rather than sour. By this means he was the first to obtain gastric juice in an approximately pure condition.

With the fluid he attempted a few experiments in artificial digestion by allowing it to act upon particles of meat at 32° R. for twenty-four hours, using meat placed in water as a control. He found that, while the meat in the control putrefied, the portions placed in the gastric juice, though not very much dissolved, were hardly at all putrefied. Hence, he concluded that digestion was not putrefaction, but something quite opposed to that process. He lamented, however, that, from the death of his kite and his neglecting to substitute other animals in its stead, he could not adduce facts sufficiently numerous to illustrate the subject more fully. He promised to supply the deficiency on some future occasion, but his death a few years

afterwards (1757) prevented him from fulfilling his promise.

Of course, these experiments of Réaumur still left a great deal to be investigated, but their value lies chiefly in the following: He employed an entirely new method in the investigation of gastric digestion. He further established the fact that the gastric liquor possessed a distinctly solvent power, dissolving various constituents of food, not by inducing or favoring putrefaction, but by a process which was quite antagonistic to it.

The next solid contribution to the subject of gastric digestion was made by Spallanzani,²³ some twenty-five years after the epoch-making investigations of Réaumur.

This scientist contributed much to our knowledge of physiology and natural history, but it is of his work upon the physiology of digestion that I wish to speak. Practically all his experiments and discussions are contained in his "Dissertations Relative to the Natural History of Animals and Vegetables," the original Italian publication first appearing in 1782.

Spallanzani's methods of experimentation were those of Réaumur, but he greatly enlarged upon them. He employed thin metallic and wooden tubes opened at one or both ends and covered with wire grating. He perforated the sides also of the tubes to allow freer access of the gastric liquor. He also used hollow brass globules divided into hemispheres, which were pierced like a sieve, and which he could open and shut at pleasure. In some cases he employed small linen sacs, using one to four thicknesses of cloth whereby he thought to partially prevent, or to increase, the action of the gastric liquor according to the thickness of the cloth. In other cases he introduced into the stomach or esophagus, meat, etc., tied to a wire or string, fastening the free end around the animal's neck. This method permitted him to withdraw the food at any time during the process of digestion, and examine it. He even introduced long cylinders containing meat, bread, etc., allowing one end to rest within the stomach and the other in the lower esophagus, and in this way was able to observe digestion in the stomach and esophagus at the same time. He employed, as did Réaumur, small sponges to obtain the gastric liquor, with which he made numerous experiments in artificial digestion. On himself he experimented by swallowing these small, thin linen bags, containing various kinds of food, examining the contents after they had been voided *per anum*. He even dared to swallow wooden tubes. Finally, he obtained gastric liquor by making himself vomit on an empty stomach before breakfast. He employed a great variety of foods in these experiments, such as grains of all kinds—wheat, corn, maize, rye, etc.; flesh of every description; also animals, including fishes, frogs and earthworms; and finally, ligaments, cartilage, hard and soft bones, teeth and coral.

²³Born in 1729, at Scandiano, in Southern Italy. He became professor of Logic, Mathematics and Greek at Reggio at the age of 25, but in 1760 was transferred to Modena, where he filled the chair of Natural History. In 1768, he became professor of Natural History at the famous University of Padua, where he labored until his death in 1799.

His experiments were very numerous and included practically all species of animals. He first investigated digestion in animals that possessed muscular stomachs or gizzards; these included common fowls, turkeys, ducks, geese, doves, and pigeons. His second dissertation deals with animals that possess the so-called intermediate stomach, namely, crows and herons. The experiments outlined in the third, fourth and fifth dissertations were performed upon animals with membranous stomachs, these including frogs, newts, earth and water snakes, vipers, fishes, sheep, oxen and horses; also, the little owl, screech owl, falcon, eagle, cat, dog, and finally man. His last dissertation deals with the question, whether food ferments in the stomach, and also with the question of the acidity of the gastric juice.

Spallanzani by innumerable experiments carried on in the various ways which I have mentioned, confirmed and greatly extended Réaumur's results. His conclusions were many, and I shall state them as briefly as possible:

SPALLANZANI'S CONCLUSIONS.

IN ANIMALS WITH MUSCULAR STOMACH OR GIZZARDS.

1. Trituration by means of the muscular walls of the stomach is the chief factor in the digestion of grains and the like, though the gastric liquor undoubtedly assists it.
2. Trituration and the action of gastric juice mutually assist each other in the digestion of flesh; the former breaking down the aliment, acts as a predisposing cause; the latter, when it is thus prepared, penetrates into it, destroys the texture, dissolves the particles, and disposes them to change their nature and to become animalized.
3. The stones that are always found in the gizzards of these animals are not at all necessary for the trituration of firm food and even harder substances, contrary to the opinion of many anatomists and physiologists, ancient as well as modern. When, however, they are put in motion by the gastric muscles, they are capable of producing some effect upon the contents of the stomach.
4. The digestion of flesh and bread may take place solely by the action of the gastric juice without any assistance from the triturating action of the gastric muscles.
5. Gastric liquor retains outside the stomach the power of dissolving animal and vegetable substances in a degree far superior to water. (He advises the use of heat and fresh gastric juice.)

IN ANIMALS WITH INTERMEDIATE STOMACHS.

1. Gastric liquor of crows is a solvent of flesh without the aid of trituration.
2. The digestion of food is proportional to the quantity of gastric juice acting upon it.
3. Bones are undigested by the gastric juice of crows, except soft ones, like cartilage, which are digested very slowly.
4. Flesh is very slowly digested by esophageal liquor.
5. Crows' gastric liquor is of a transparent yellow color, which deposits very little sediment on standing, possesses a bitter and salty taste, has very little volatility and is non-inflammable.
6. Gastric juice, outside the body, digests flesh without the production of putridity. Digestion is enhanced by heat and is more rapid when gastric liquor is allowed to flow slowly over the flesh and constantly renewed. Digestion is retarded by cold.
7. Gastric juice is secreted by small arteries, which open into the stomach. (He was not sure of the presence of any gastric glands which might serve such a purpose.)

8. Some power of trituration is present in the stomach of the heron, but digestion here is not the effect of the trituration, but of the solvent power of the gastric juice. It has even the power of digesting bones.

9. The bitter taste of the gastric liquor derives its origin from the bile which regurgitates through the pylorus into the stomach cavity.

IN ANIMALS WITH MEMBRANOUS STOMACHS.

1. In frogs, gastric juice was found to have slow digestive powers.
2. Water-newts digest fish-worms in twenty-four to forty-eight hours without the intervention of trituration.
3. Digestion of food in frogs, serpents, water snakes, vipers, eels, carps, barbel and pikes is performed by the gastric juice, though somewhat slowly. No trituration is present.
4. In sheep and oxen the process of rumination precedes the solvent action of the gastric liquor. No triturating power is present.
5. The gastric fluid of the little owl can digest bones as well as flesh. It does not become putrid even when exposed for months in hot weather. Esophageal liquor from this animal also digests flesh quite rapidly. (He obtained similar results with the tawny owl.)
6. The gastric juice of the falcon digested bone and tendon quite rapidly, as well as flesh, but did not have much effect upon teeth, enamel or horn. Trituration is not a factor.
7. In the eagle such substances as bread and cheese and flesh and even bone were quite readily acted upon by the gastric juice outside of the body. The gastric juice of this bird digested animal and vegetable substances. It produced an incipient solution of bone and almost a complete one of cartilage.
8. The gastric fluid of the dog and cat is the efficient cause of digestion in these animals, independently of any triturating power. In the dog it also acts upon bone, but not so speedily as upon flesh, because of its hardness.
9. There is a peristaltic motion of the stomach of dogs and cats and some other animals, which was demonstrated by opening the abdomen shortly after feeding. It was easily excited by irritating the stomach with a knife point, which produced contraction followed by an undulating wave across the stomach and by a dilatation of the contracted portion. This gradual movement of contraction and dilatation began at the upper end of the organ and extended to the lower and (he felt that) this motion was calculated, not to triturate the food, but to carry it slowly from the superior to the inferior orifice of the stomach, and thence to expel it into the duodenum.
10. In the experiments upon himself he found that flesh and bread were rapidly digested by his gastric juice independent of trituration, and that it could dissolve muscle fibres, membrane, and even tendon, cartilage and soft bone, though the time consumed in digesting the latter substances was somewhat longer than in the case of the former. "Before quitting the subject," he says, "let me observe that though I have mentioned the gastric juice as the efficient cause of digestion in the experiments upon myself, yet I mean not to exclude those of the intestine from their share. We know that the small intestine completes the process of chylification, which is but begun in the stomach. I must allow, therefore, that the digestion of animal and vegetable substances in the bags and tubes is perfected in the intestine. But this is not in the least repugnant to the results of those experiments that show the human stomach to be destitute of any triturating force, and digestion to be the effect of the gastric juice alone, though the fluid which is secreted by the side of the small intestine may complete the process."
11. The gastric fluid obtained from his own stomach was a little salty to the taste but not especially bitter, and possessed no prop-

erty of inflammability. Gastric juice left in a phial one month did not become putrid. Beef was quite readily dissolved when kept at a definite heat and did not putrefy, but the control in water became excessively putrid in a short time.

12. The gastric juice is probably provided with an antiseptic principle. When acting upon flesh, etc., outside (or inside) of the body, it rarely, if ever, putrefies. In fact, it impedes putrefaction and in some cases may even restore putrefied substances. None of the three species of fermentation (sweet, acetous or putrid) takes place in digestion.

13. There is present in the stomach of man and some animals an acid principle, but it is not constant and depends on the quality of food. This temporary acidity is not produced by the gastric fluid, but by the food. (He sent a specimen of the crow's gastric juice to Scopoli, the eminent chemist, for analysis—apparently the first detailed analysis on record. The results of this and his own examination led him to the conclusion that the gastric fluid was neither acid nor alkaline, but neutral. He thinks, however, that there may be a latent acid in this fluid, though it cannot be detected by any of the ordinary means. His reason for this was the observation that it readily curdles milk—a fact held by Macquer and others to be a sign either of a manifest or occult acidity.)

We thus owe to Spallanzani, after Réaumur, the definite experimental proof of the solvent power of the gastric juice upon various constituents of food, but he was unable to go much beyond this, because he failed to recognize its acid character. He, however, conclusively disproved the older theories of digestion, especially that of trituration, putrefaction, fermentation and maceration.

I have dwelt at some length upon the investigations of these two men because it seemed to me that they were pregnant with many suggestions for future scientific lovers of truth. Their work is in reality the germ from which many of our more modern ideas concerning the physiology of digestion have sprung. During the next fifty years numerous monographs appeared dealing with various phases of digestion, and I deeply regret that I could not have brought the subject up to a more recent date. But, before closing, it might be of interest to mention briefly some of the more important additions which were made during the half century following the work of Spallanzani.

In his physiological inaugural dissertation, entitled "De Alimentorum Concoctione," Stevens of Edinburgh, in 1777, adopting the methods of Réaumur, substantiated the work of the French and Italian inquirers. In 1772, appeared a paper by John Hunter, published in the Philosophical Transactions, "On the Digestion of the Stomach after Death." This was followed, in 1786, by his "Observations on Digestion," both of which papers contain many interesting facts and observations relative to our subject. It is very evident, from a perusal of these articles, that Hunter entertained views on digestion which are very similar to those of Spallanzani, though modified by the vitalistic Stahlian conceptions, in which the latter did not share. Hunter at first was inclined to attach considerable importance to the acidity of the gastric juice. In 1772, he writes, "In all the animals, whether carnivorous or not, upon which I made experiments to discover whether or not there was an acid in the stomach (and I tried this in a great variety), I constantly found that there was an acid, though not a strong

one, in the juice contained in that viscous in a natural state." But in his later communication he says, "It is only found occasionally." And, indeed, the 18th Century passed wholly away before the "acid ferment" on which van Helmont had, in the early years of the 17th Century, laid such great stress was rightly appreciated; for the observations of Carminati, who in 1785 found the clue to the problem of the acidity of gastric juice, by showing that in carnivora at least the juice, though neutral when the animal is starving, is undoubtedly strongly acid after it has been fed, fell on barren ground.

We have seen that numerous theories as to the nature of the digestive process, before the time of Spallanzani, were held by physiologists. That of *coction* was entertained by Hippocrates, Galen and others; *putrefaction* by Praxagoras of Cos, and apparently, even by Chelseden (1688-1752); *trituration* by Erasistratus, Redi, Borelli, and others; while the theory of *fermentation* had many partisans, amongst whom may be mentioned, van Helmont, Sylvius, Willis, Grew and Lower. Even Haller adhered to the theory of maceration, supposing that the food is merely diluted and softened by the stomach fluids. Finally, we have the theory of *chemical solution*, proposed by Spallanzani, a theory which met with more favor from physiologists than any of the others.

To such a turbulent state of knowledge, the well known pithy and laconic observation of William Hunter was certainly not out of place, "Some physiologists will have it, that the stomach is a mill, others that it is a fermenting vat; others again, that it is a stew-pan; but in my view of the matter, it is neither a mill, a fermenting vat, nor a stew-pan, but a stomach, gentlemen, a stomach."

In 1803, Young, of Baltimore, experimenting upon frogs, snakes, and other animals, demonstrated that the solvent power of the gastric juice is due to its acid content, which turned litmus paper red. He further showed that it had its origin in gastric secretion, and that it did not originate from any kind of fermentative process, vinous or otherwise. He also deduced the important fact that the flow of gastric juice and saliva are associated and synchronous, a point which has but recently been demonstrated by Pawlow and his collaborators. He made the error, however, that it was phosphoric and not hydrochloric acid that was present. It was not until twenty years later (1824) that Prout (1785-1850) of England proved that hydrochloric acid was the free acid in the gastric juice.

Prout was speedily followed and his statement affirmed by Tiedemann (1781-1861) and Gmelin (1788-1853) in their notable monograph "Die Verdauung nach Versuchen," which appeared in 1826-27.

Six years later, in 1833, there was issued from the press a volume entitled, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion," which contains the classical and far-reaching investigations of William Beaumont (1785-1853) a surgeon of the United States Army, upon the young Canadian voyageur, Alexis St. Martin, who was accidentally shot in the stomach (1822), the wound healing after a year or more with the production of a gastric fistula,

the aperture being about two and one-half inches in circumference. Beaumont at once seized the opportunity which presented itself in this remarkable case, and at different periods during the following nine or ten years he performed numerous experiments, 238 in all, with this Canadian half-breed as the subject of his investigations.

Several cases of artificial gastric fistula had been reported before the time of Beaumont's work, but the case in point stands out pre-eminent above all others on account of the accuracy and care with which the experiments were performed.

As we have seen, much uncertainty existed in the minds of men as to the exact nature of the phenomena occurring during digestion in the stomach, the precise mode of action of the juice, the nature of the juice itself and its action outside the body. On all these points Beaumont's investigations brought clearness and light where there had been previously the greatest obscurity. Perhaps, the most important observation was his study of the digestibility of different articles of diet in the stomach, which remains to-day one of the most important contributions ever made to practical dietetics. His observations are probably the most important ones until the time of Pawlow and his school who, chiefly by perfection in technique of experimentation, were able to carry the work further. Beaumont was truly the leader and pioneer of experimental physiology in our own country.

In looking back over the centuries and tracing the historical development of the various systems and theories which were formulated from time to time by the greatest physicians, scientists and philosophers of their day, we are unable at the present time to appreciate at their true value the circumstances under which they were formulated, and the advantages or disadvantages attendant on their conception. But it must remain an element of surprise and disappointment that the views current up to the close of the 18th Century should show so slight an advance over those formulated, with less particular knowledge, two thousand years before.

No less surprising is the wonderful advance which has been made since the beginning of the 19th Century in the elucidation of physiological problems. Coincident with the onward progress of science our knowledge of the chemical and physiological processes which serve to support life has remarkably increased. Thanks to the patient investigation of the infinitely little, and to the gathering together of the results, theories of

vital processes can now be based upon multitudes of observed facts, giving both positive and negative evidence.

By following the teaching of Hippocrates in 400 B. C., teaching which was until lately disregarded, or at least spasmodically and superficially followed, we have penetrated many of the mysteries connected with bodily processes, though much still remains to be done.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

JANUARY 3, 1916.

1. Seminal-Vesiculectomy in Arthritis. DR. H. H. YOUNG.

DISCUSSION.

DR. QUINBY: I can only call your attention to one or two further points with regard to the seminal vesicles. I have felt that the development of the surgery of these organs is a subject of which American surgeons should be very proud, because, although they

were described, as were so many other structures of the human body, by Fallopius in the sixteenth century, and of course were known by all subsequent anatomists and surgeons who were not afraid to attempt surgery on them, still it remained for American surgeons, and above all for the present generation of American surgeons, to demonstrate a successful surgical approach to these organs. As one looks over the literature of the subject to-day one finds instead of a long list of German, French, Italian, Polish, and Russian names, that the contributors are almost entirely American. This is due to the fact that American ingenuity was applied at the time when the European surgeons had given up serious, radical

attempts on these organs. The work, as Dr. Young has mentioned to you, was started first in this country by Dr. Belfield of Chicago, and by Dr. Fuller of New York, but it was not until such deft operators as the president of this society directed our attention to the subject, that successful excision of the vesicles was made possible.

Some may ask if the seminal vesicle, when normal, is of any special value except as a reservoir; or whether it has some function which should be preserved if possible. For a good while the idea prevailed that the vesicle was simply a reservoir for portions of the spermatic fluid. More recent physiological observations, especially on animals, have shown that, though this is true, it has other intrinsic functions. In some species the secretion of the seminal vesicle has agglutinating properties. For instance, in the rodents, more especially in the guinea-pig, the secretion of the seminal vesicle causes the prostatic secretion to coagulate. By this method nature provides in two ways for successful impregnation. By coagulation the material is prevented from leaving the vagina after coitus, while at the same time the spermatozoa are squeezed outside the coagulum so that they can exert their normal activity unhampered. In various other ways also the secretion of the vesicle is important. For instance, it has been shown that reproduction is not impossible after extirpation of the vesicle, but that the fruitfulness of such an animal is decreased.

I quite agree with Dr. Young's conclusions that if one is operating on a vesicle which is so diseased as to necessitate exploration, it should be removed in the large majority of cases.

DR. HUNTER: It does not seem necessary to emphasize the importance of this subject—the rôle played by the genito-urinary organs in furnishing a focus for widespread infection. In the female we do not see many cases in which arthritis can be traced directly to the genito-urinary organs. Of course, the genitalia have the deep glands of the cervix and the Fallopian tubes, which, becoming infected with gonococci, occasionally form foci for infections of the joints. In the urinary tract we do not have to deal with the deep glands characteristic of the male, and for that reason we see far fewer cases of general infection or arthritis derived from the urinary tract of the female.

I have been particularly interested for the past few years in infections which come to the genito-urinary tract from other foci, such as tonsils, teeth or sinuses. I hope in a short time to bring before the society a series of 50 cases of stricture of the urethra, in a good many of which, I am satisfied, the infection that started the infiltration about the urethra came from some distant point, such as the tonsils, teeth or sinuses.

I have been interested in the male side of this question, more particularly because of the women who have come to me complaining of sterility. It seems strange that, even to-day, women go about from gynecologist to gynecologist being treated and cured because they are sterile and anxious to become pregnant, while the logical and simplest method of finding out what the real trouble is in a good many cases is to have the male examined. In from 40 to 50 per cent of these cases, on examining the secretions of the male, we find the sterility in all probability is due to blocking or obstruction of the spermatic organs.

Certainly those interested in genito-urinary work in the male will feel a great debt of gratitude to Dr. Young for these methods which he has presented to us to-night.

DR. GUTHRIE: It is, of course, a matter for congratulation that another possible focus of infection has been discovered. We have felt for a long time that there were foci that were not being approached, and particularly ones which were apparently cryptic and which do not present symptoms which would lead to suspicion being cast upon them. One great difficulty which is encountered by all those who try to arrive at a diagnosis in infectious arthritis

is the multiplicity of possible foci and sometimes of actual foci which may exist. The question then arises as to which one is the seat of the trouble. In a recent case on the wards, the patient was discovered to have abscesses about the roots of the teeth. Despite the protests of the patient, these were removed. The next thing was an examination of the sinuses and the remains of the tonsils. One diseased tonsil was discovered and also eliminated. Following that an examination of the digestive tract revealed a difficulty about the appendix. This was investigated and, the suspicion that there had been trouble in this area having been confirmed, the appendix was removed. Following each one of these procedures, the patient improved considerably, but I have a letter to-day saying that her symptoms have returned. Apparently the search for the guilty focus must be resumed.

2. Tuberculosis of the Tonsils. DR. S. J. CROWE.

JANUARY 17, 1916.

1. Methods and Results of Direct Transfusion. DR. R. D. McCLEURE and DR. GEORGE DUNN.

To appear later in the BULLETIN.

2. The Clinical Significance of the Wassermann Reaction. DR. ARTHUR F. COCA.

DISCUSSION.

DR. MILLER: I am extremely interested in the message brought this evening. It brings up the question in one's mind as to whether the Wassermann reaction is worth anything, or any treatment is worth anything in lues. From the scheme drawn on the board, I am not prepared to answer, off hand, which of the conclusions one can justly arrive at.

There are a few points I would like to take up briefly. First, Dr. Coca made the statement that the reagents employed in the Wassermann reaction are very unstable and vary from day to day. I think that is open to some argument. Patients' serum is an unknown variant. The amboceptor which has been suitably prepared has, I believe, usually been regarded as quite a stable thing. That is, given an amboceptor of a given titre, it does not vary much from time to time provided it is kept under suitable conditions. The suspension of sheep's red blood cells, freshly prepared, is a presumably stable reagent. Each new lot of complement is stable during the period in which it is used, and its power is determined by suitable preliminary titrations. Any given antigen suitably titrated from time to time is constant, in that you know what it will do, at least relatively. If, however, one takes the various short cuts designed to be useful and time saving, then a number of these preliminary titrations are omitted and one is dealing with a number of variable reagents, and presumably some of them at times are absolutely inert. So I should think a possible criticism of the statement of their variability might be taken into consideration from that standpoint. Out of the first 1200 cases admitted to the Phipps Psychiatric Clinic, all cases were routinely tested against three different antigens—the cholesterolized extract of human heart (.04 cholesterolin), a similar extract of the same heart not cholesterolized, and the acetone insoluble lipid fraction prepared according to the Noguchi method. These were all tested for their binding powers, and we knew what each antigen would do in terms of the other two. Out of the first 1200 cases, the results with these three different antigens, in all cases of known, unknown or suspected lues, were identical, except in seven cases. In those seven, the cholesterolin extract gave a positive fixation, while the other two were negative. This was in our minds suspicious enough to warrant the repetition of the Wassermann on those individuals' blood taken a week later, and also a control done by someone else who had known nothing about the condition. In all seven instances, the result came back the second

time exactly the same and was confirmed from one or two other sources. In my experience even two antigens are not enough to be invariably useful, for there are differences between antigens that apparently bind equally well with a known positive serum, which we do not yet know.

As regards the one particular point that interested me most—the finding of the uselessness of the Wassermann reaction in non-luetic and in unsuspected cases—it seems to me that there may be fallacies (and I am not by any means certain that the Wassermann reaction is free from fallacies), yet all the weight of evidence is against the statement. There have been too many instances where a definite luetic process has been confirmed by the subsequent course of the case, either at autopsy or by following suitable therapy. I do not believe that the Wassermann reaction is a biochemical one. I believe it will be shown to be a purely chemical process, essentially a colloidal chemistry affair. There is evidence for this that has apparently been buried away in the literature. It has been definitely suggested by Paul Schmidt that the sera of luetics differs colloiddally very markedly from the sera of normal individuals. It seems to me that discrepancies in results will ultimately be explained on the basis of colloidal chemistry. I simply throw out the suggestion as being a possible source of hope in this apparently hopeless tangle.

DR. KEIDEL: I would like to say that I agree with Dr. Miller's remarks on the various reagents that we use; and to add that with our titration of the complement I think we can always eliminate that as a source of error, provided we maintain a high standard for it. We have always felt that we must be continuously making new antigen preparations. While we do not adopt a unit of titre, we, nevertheless, use a comparative method of investigating them. We run more than one antigen in the series and try always to have a new antigen running with the others. If the new one does not come up to the standard of the antigens we have been using, we discard it. In this way we keep up an antigen standard which it seems to me must always be, if anything, slightly on the increase so far as efficiency is concerned. These antigens, of course, are always controlled for objectionable qualities such as would give a false positive. There are differences which have not been mentioned so far, which might account for some of the lack of uniformity in results, for we have observed that the sera of syphilitic patients reach a stage, particularly in treated cases, where there is a great variation from day to day in the amount of fixing body in the sera, that is to say, there is a zone in which the patient may vary, so that one day his sera may contain more fixing bodies, sufficient to give a positive Wassermann, and another day these may fall, so the Wassermann result would be a doubtful reaction. Another time they may fall so low that the reaction is completely negative. We have seen this repeatedly, in fact in almost all our treated cases this variation occurred. This would not, of course, be brought out unless a great many tests were made. We make frequent Wassermann tests. Our patients on treatment are in many cases tested every week, and always once a month.

With regard to the indictment of the Wassermann reaction, I do not think we are prepared to agree here with Dr. Coca's list of answers. We would certainly treat a typical hard chancre, with a history and with no secondaries, although the spirochetes are absent. In the first place such a lesion might easily not have spirochetes, because we know they tend to decrease in number as the lesion tends to heal, so that, even though the chancre may be typical, it may be perhaps at a late period, and we might fail in such a case to get spirochetes. In the second place, we know from experience here, and I am sure they do in other places, that the effect of treatment, particularly that of salvarsan, is so striking that we can make a diagnosis of a chancre practically by that alone, and with that as an aid we find we are justified in reading a positive Wassermann as an indication for immediate treatment in those cases. In such a case with a negative Wassermann, while

the chancre may appear to be a typical one, we have still to remember that it may be a chancre redux or a tertiary lesion. Some cases of chancre I am sure are overlooked which at least should be recognized as chancre redux. In those cases there would be no spirochetes, and, the lesion being tertiary, there might be a negative Wassermann. I would be in favor of treating those cases at least as a diagnostic means.

In the second group of cases, we probably agree. In cases of typical chancre and secondaries, we would undoubtedly treat under A. Under B we would treat tentatively at least, with the idea that if we got no result from treatment, we would suspect some other condition.

In the third instance, we would not treat, because we would insist upon having a Wassermann test first. In the third group, we make our diagnosis clinically, regardless of the Wassermann reaction, if we feel sure enough to diagnose a lesion as a tertiary syphilide. There is a chance, of course, that the Wassermann may be negative in about one-third of the cases. If we made a diagnosis clinically, we would undoubtedly treat the case whether the Wassermann was positive or not. In obscure cases, I can only say this, that several years ago I analyzed with Dr. Frontz some 4000 cases in which we had made Wassermann reactions for diagnosis. We divided our cases into several groups according to the history and manifestations. Each group was subdivided into treated and untreated cases. While I am sorry to say I cannot give the figures exactly, I can state, however, that as the presumptive evidence of syphilis increased from group to group, so did the presence of the positive Wassermann. In the groups of treated cases there was always a lower percentage of positive Wassermans than in those untreated. This analysis showed us that, when using the Wassermann reaction as an aid to diagnosis in a large series of cases, the percentage of positive Wassermans increased as the evidence in favor of syphilis increased.

I quite agree with Dr. Coca that it is an extremely difficult matter to pick out non-syphilitic cases and test them and get 100 per cent negative. There are bound to be so-called clinically latent cases which would fall in that group and give a positive Wassermann. In the treated cases, there is difficulty, because we use the Wassermann as an indication for treatment as long as it is positive. If the Wassermann reaction becomes negative, we have lost a means of following the effect of the treatment. Our rule here, as a general thing, although we do not regard the degree of positiveness of the reaction as an indication of the severity of the disease, is to give a patient treatment and follow his Wassermann at frequent intervals. We know the time necessary to produce a negative Wassermann and use that as a basis on which to figure the amount of treatment that patient should have subsequently. The Wassermann undoubtedly then is of great assistance in treating those cases.

DR. MILLER: In this series of 112 cases in which the same two antigens were used by all five observers, it would be interesting to know if all five observers used a uniform technique. I think that makes a very material difference. It can readily be demonstrated that, given the same two antigens, two people in the same room at the same time, by different methods of mixing the antigens with salt, may get diametrically opposite results. Therefore, the series to have been of any value must have been comparatively the same all the way through, or else it cannot hold.

DR. COCA: There is only one question that I have to answer—the question of Dr. Miller with regard to the technique used by the different men. You can anticipate what the answer will be—that it was humanly impossible for each one of these men to be under constant supervision in order to see that they did not put one thing in before the other, or the other before the one. It is, however, significant that Dr. Miller admits that two men standing side by side, using the same reagents, may get opposite results. His statement agrees with practically everything I have said.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

JANUARY 10, 1916.

1. Jonathan Letterman and His Work in Organizing the Medical Department of the Army of the Potomac. DR. JOSEPH T. SMITH.

To appear later in the BULLETIN.

2. William Hunter, Anatomist, Physician, Obstetrician. DR. C. W. G. ROHBER.

To appear later in the BULLETIN.

THE LAENNEC.

JANUARY 24, 1916.

Memorial Meeting to Dr. E. L. Trudeau.

The proceedings of this meeting appeared in full in the April number of the BULLETIN.

NOTES ON NEW BOOKS.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles on Treatment of Medicine, Surgery, Neurology, Pædiatrics, Obstetrics, Gynecology, Orthopædics, Pathology, Dermatology, Ophthalmology, Otology, Rhinology, Laryngology, Hygiene and Other Topics of Interest to Students and Practitioners, 1915. Vol. III. Twenty-fifth Series. (Philadelphia: J. B. Lippincott Co.)

It is not clear why the title "Clinics" should be applied to it, in view of the fact that fully one-third of the present volume is not in any sense clinical or even remotely connected with bedside practice. The papers entitled "One Hundred Thousand Men Minus," "The Ideal Physician as the Citizen-BUILDER," "The Advantage of a Library to a Medical Society," "Sanitation Among the Indians," "Defects in Our Public Insane Hospitals," "Medicæval Medicine and Medical Reform," "The Case Against Neo-Lamarckism" and "Therapeutic Technic" are interesting and profitable, but give one the impression of being essays originally prepared for another purpose, which have been "commandeered" by the enterprising editor. The sections dealing with Diagnosis and Treatment, Pædiatrics, and Surgery, contain many admirable papers, of rather unequal length, but all worthy of attention.

Diseases of the Skin and the Eruptive Fevers. By JAY FRANK SCHAMBERG, A. B., M. D. Price \$3.00. (Philadelphia: W. B. Saunders Co., 1915.)

There is always a place for a text-book which fulfills certain requirements. There are, of course, numerous excellent and satisfactory text-books on dermatology in English, by American authors, and it would seem that the addition of another would be entirely superfluous. It is well known that the complete text-book is of greatest use to the dermatologist himself, and that for the practising physician it is at times too comprehensive and encyclopedic in character. The kind of book which presents the subject briefly, clearly, and practically, both for the busy doctor and especially for the eager medical student is always welcome. The medical student has not the time, the energy, nor even the enthusiasm, to read a complete and comprehensive contribution on a dermatologic subject. For him especially, a short, readily comprehended, and even somewhat dogmatic, presentation is most acceptable and therefore most impressive. It is for this reason that a book like Schamberg's finds a most welcome place.

The entire subject matter of dermatology is covered and, in addition, there are sections on opsonotherapy, actinotherapy,

radiotherapy, serologic procedures, and the acute eruptive fevers, including about a dozen acute infectious diseases accompanied at times by eruptions.

It is realized that a book of this kind must sacrifice much to brevity; yet it is to be regretted that the author has not written more fully on symptomatology in general, and on the rationale of treatment. A somewhat fuller discussion of the pathology of some of the commoner diseases would be advantageous from the standpoint of a more appreciative understanding on the part of the reader. For example the pathology of acne vulgaris is described in four lines. The discussion of X-ray therapy, which the author acknowledges has become such an important part of dermatologic therapeutics, is excellent, though not complete, since there is no guide to dosage, which after all is the principal point to be considered.

The text is well written; the illustrations are for the most part excellent; but, here again, it is to be regretted that more could not be used. The type is excellent, and the volume handy and attractive.

Especially noteworthy are the author's opinions, well and frankly expressed, on etiology and on therapeutics in particular—the things which give individuality to a text-book. He gives many prescriptions used in his own practice, written also in the metric system, and (fortunately for the student who is somewhat backward in prescription writing) written in full. He has presented a very sane conception of the treatment of eczema in general. The presentation of syphilis is excellent, even if not entirely comprehensive. Perhaps the most valuable contribution is the section on the acute exanthemata, on which the author is eminently qualified to write. The section devoted to eruptions associated with internal diseases forms a very desirable portion of the book and gives a very satisfactory conception of this very important part in the symptomatology of such diseases.

This book, therefore, should find a place in a field which is already replete with splendid contributions from American dermatologists.

I. R. P.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Vol. III, September, 1915: Diseases of the Thorax, Heart, Lungs, Blood Vessels, Skin, Nervous System, Obstetrics. Vol. IV, December, 1915: Diseases of Digestive Tract, Genito-Urinary Diseases, Surgery of Extremities, Diseases of Kidneys, Therapeutics. (Philadelphia and New York: Lea & Febiger.)

These volumes maintain the high character of the previous issues and contain interesting and valuable discussions on questions of the day, among which may be mentioned surgical shock, anæsthesia, infections, fractures, gastric and duodenal ulcer, and diseases of the kidneys. The various papers cannot be reviewed in *extenso* because of the great variety of topics which they cover, but are worthy of careful attention on the part of physicians and of students of medicine.

Applied Immunology. By B. A. THOMAS, A. M., M. D., and R. H. IVY, M. D., D. D. S. Price \$4.00. (Philadelphia: J. B. Lippincott Company, 1915.)

This is a publication of 350 pages devoted to practical immunology, that is, to the methods employed in the preparation and administration of antitoxins, antibacterial sera, and vaccines. A mass of detailed information is presented in a systematic way and in general the author's aim of furnishing the medical profession with an exact knowledge of immunology and its conservative conclusions may be said to be fulfilled. The unfavorable results so often following the injection of vaccines are clearly brought out and the book will undoubtedly have a strong influence in combating the indiscriminate use of commercial preparations by practition-

ers of limited experience. We wonder if it is wise, however, to make such positive assertions as that on page 295, "Were the practice (typhoid vaccination) universal, typhoid fever would soon cease to exist." Certainly not, until methods have been established whereby individuals vaccinated against typhoid fever are more surely protected than at present seems to be the case. Nor does it seem proper to advocate the Coley treatment of sarcoma by the injection of "the streptococcus of erysipelas and bacillus prodigiosus," as is apparently done on page 303. A more extended experience of the medical profession in the field of practical immunology may clear up many doubtful points, and it may be hoped that in a future edition the authors will be able to tell us just what vaccines are of value and how far physicians are justified in administering them.

W. W. F.

Alveolodental Pyorrhea. By CHAS. E. BASS, M.D., and FOSTER M. JOHNS, M.D. Illustrated. Cloth, \$2.50 net. (Philadelphia: W. B. Saunders Co., 1915.)

This book has evidently been written by enthusiasts whose treatment of this disease, and clinical data, have been limited. The deductions drawn are not borne out by Koch's law; in fact, they are contradictory to it.

Endameba buccalis is not recognized by investigators of acknowledged ability as an established etiological factor, its pathogenicity being seriously questioned. The clinical observations advanced in support of the treatment suggested are not sufficiently well founded, and it would seem that no justification exists for bringing this method into general use.

The practical value of this book to either the physician or dentist is questionable.

L. D. C.

Trachoma—Its Prevalence, Its Effects Upon Vision and the Methods of Control and Eradication. By GORDON L. BERRY, Field Secretary, National Committee for the Prevention of Blindness. Price, \$40.00 per thousand. (New York: National Committee for the Prevention of Blindness, 1915.)

A most interesting and instructive pamphlet, and, although written by a layman for the general public, contains a great deal that even the oculist can read with profit.

The illustrations, all from photographs, are unique and illuminating, and the statistics showing the virulence and wide distribution of the disease in this country will be a great surprise to almost everybody.

H. H.

Lead Poisoning. By SIR THOMAS OLIVER, M.A., M.D., M.R.C.P. Cloth, \$2.00. (New York: Paul B. Hoeber, 1914.)

This little volume on lead poisoning, by Sir Thomas Oliver, is the book form of the lectures on this subject delivered in the Royal Institute of Public Health, Russell Square, London. Ever since the discovery, by Dr. George Baker in 1767, that the "colic and pals" common among the inhabitants of Devonshire, especially in those addicted to the use of hard cider, was simply lead poisoning, English physicians have been keenly alive to the danger that lead offers to the British workman.

These lectures give in a readable and pleasing manner the present state of knowledge on the subject. The subject is treated chiefly from the clinical standpoint and the book is singularly free from the dry statistical tables so often observed in works on industrial diseases. Of especial value is the closing portion which gives in detail the various regulations enforced in English factories for the prevention of saturnine intoxication.

W. W. F.

Fever, Its Thermotaxis and Metabolism. By ISAAC OTT, A.M., M.D. Price \$1.50 net. (New York: Paul B. Hoeber, 1914.)

This book consists of the collected lectures of Dr. Isaac Ott, delivered before the Sophomore Class of the Medico-Chirurgical College of Philadelphia. They form most interesting reading and enter in detail into the causes and metabolism of fever. The literature is most completely reviewed and referred to throughout the lectures. The various centers in the brain for the control of heat regulation are given and the experiments employed in their exploration presented in detail. Having finished up the discussion on thermotaxis or heat regulation in the first lecture, in the second, he takes up thermolysis or heat dissipation. Here again a description of numerous interesting experiments and descriptions of calorimeters is given. The third lecture contains a lengthy study of malarial fever in relation to the metabolism of fever and an account of certain investigations of this disease. Last of all, general metabolism in fever is considered in detail. The book on the whole provides interesting reading, although the personal pronoun is used a little more frequently than is necessary.

J. A. C.

Gynecology of Obstetrics. By DAVID HADDEN, B.S., M.D. Cloth, \$3.50 net. (New York: The Macmillan Company, 1915.)

There is nothing in this work which cannot be found much more compactly and accurately in the average text-book of gynecology. According to the author it is "an exposition of the pathologies bearing directly on parturition," but there is practically no reference to adnexal or uterine disease. The anatomy of the perineum and cervix, and the discussion of the various symptoms resulting from lacerations and their relief by operative treatment, occupy most of the 187 pages. The subject matter is quite commonplace and there is nothing new that is of scientific interest. There are many inaccurate statements that still further detract from its value. The author has attempted to explain the greatest variety of conditions as being due to perineal and cervical injuries and this attempt has led to many statements that are, to say the least, questionable.

Many of the illustrations are reproductions of micro-photographs and these are excellent. The colored photographs of the dissections of the pelvis are nicely executed, but are not to be compared with the usual semi-diagrammatic representations of anatomical material.

E. D. P.

Therapie der Haut- und venerischen Krankheiten. By PROF. DR. J. SCHÄFFER. Cloth. Price 10 marks. (Berlin: Urban & Schwarzenberg, 1915.)

The chief value of this small volume lies in the first part, which deals with the general principles of therapy. Here the author takes up many of the seemingly small things, such as the way in which to apply medicaments, the cleansing of the skin before and after local applications, etc., which are so very important in treatment and which are most frequently not sufficiently emphasized in larger texts.

An attempt to arrange drugs in scales according to the intensity of their various activities is more didactic than practical, but will serve as a working basis for the student.

The part dealing with special therapy has nothing to recommend it above many other books of this character; and the fact that so many of the drugs advised are of a proprietary nature, and are expensive and difficult to obtain in America, renders the book, from the standpoint of prescriptions, of less use to the practitioner than one published in our own country.

L. W. K.

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THORIUM—A NEW AGENT FOR PYELOGRAPHY.¹

By J. EDWARD BURNS, M. D.,

Assistant Resident Urologist, James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Balto., Md.

Ever since the introduction of pyelography by Voelker and Von Lichtenberg² in 1906, its prime importance in the rôle of renal diagnosis has readily been recognized. Although various attempts have been made to replace collargol, the medium recommended by them for injection, it has proven the pyelographic agent par excellence up to the present time. The various colloidal solutions of salts of heavy metals, which have been tried as substitutes, are those of silver, iron, bismuth, copper, lead and mercury, as have suspensions of the salts of bismuth, calcium and magnesium. All of these solutions sediment on standing, and while being for the most part quite opaque to the Roentgen ray, are viscous; moreover, a great many are quite toxic and irritating.

The chief objection to collargol is its irritant action when it escapes into the tissues, and, as a matter of fact, there have been

a number of deaths reported following its use. Its elimination from the urinary tract is somewhat prolonged on account of its viscosity. The fact that it stains everything with which it comes in contact makes it objectionable. It is also quite expensive; for this reason its use for cystograms and large hydro-nephroses is often prohibitive.

An ideal solution for use in pyelography should be non-toxic, (within the ordinary limits of usage) non-irritating, quite opaque to the Roentgen ray, and give not only a good shadow but one of clear delineation; it should possess a marked degree of fluidity, permitting its ready escape from the urinary tract, and be inexpensive so as to be generally used.

Since the opacity of a substance to the Roentgen ray depends upon its atomic weight, thorium, being next to the heaviest known element, was quite ideal theoretically and seemed worthy of careful investigation.

The nitrate and chloride of thorium are quite readily soluble in water, giving a clear, markedly acid and astringent solution. These solutions precipitate insoluble salts in the urine and also precipitate proteins, this latter characteristic making impossible their intravenous introduction in greater degrees of concentration than two per cent. These solutions are also quite irritating. All of these qualities render them unfit for clinical

¹ A Preliminary Report on "Thorium—A New Agent for Pyelography" was published in the J. A. M. A., Vol. LXIV, pp. 2126-2127. This paper was read before The Johns Hopkins Medical Society, Feb. 21, 1916. From the James Buchanan Brady Urological Institute.

² Voelker & Von Lichtenberg; "Pyelographie (Röntgenographie des Nierenbeckens nach Kollargolfüllung)" Münch. med. Wehnschr., 1906, LIII, 105-107.

use. However, on account of the ready solubility of these salts, a very concentrated solution can be made, the nitrate having been used in as high concentration as fifty per cent (Fig. 1). These solutions are particularly valuable for the injection of pathological specimens, the finest hair-line vessels and ducts being readily seen in the roentgenograms of these specimens. The plate below (Fig. 2) shows the seminal vesicles, ampullæ and vasa deferentia, injected with a fifteen per cent solution of thorium nitrate. After this injection the specimen was fixed in Kaiserling's solution, which latter caused a precipitation of thorium salts in the walls of the ducts, markedly accentuating their outline in the roentgenogram.

Regardless of the fact that the above mentioned properties render these salts unsuitable for clinical use, it is quite evident that thorium in some form would be ideal for use in pyelography. It is very well known, however, that different salts of the same metal vary greatly in their irritating and toxic action, these latter characteristics seemingly varying indirectly with the size of the molecule, and being sometimes especially reduced in a complex ion formation. After a careful series of chemical studies of the various combinations into which thorium may

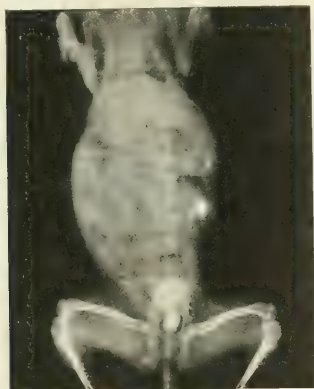


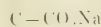
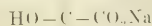
FIG. 1.—Renal pelvis and ureter of rabbit injected with a 50 per cent solution of thorium nitrate.

enter, a solution containing a double citrate of sodium and thorium, together with an excess of sodium citrate and some sodium nitrate, was found to possess the qualities enumerated above as being necessary for an ideal pyelographic medium. The solutions used contain ten per cent and fifteen per cent of thorium nitrate, and are made in the following way:

To make 100 cc. of a ten per cent solution, 10 gm. of thorium nitrate are dissolved in as little distilled water as possible; to this solution, kept hot on a water or steam bath, are added 30 cc. of a fifty per cent solution of sodium citrate, the additions being made in small quantities, and care being taken to shake the solution thoroughly after each addition. At first, after the addition of the citrate solution, a white gummy precipitate is formed, which later becomes granular, and finally dissolves on the addition of all the citrate solution. This solution is

then made neutral to litmus by the careful addition of a normal solution of sodium hydroxid, and made up to the required volume of 100 cc. with distilled water. On filtration, a clear, limpid solution is obtained, which, when sterilized, either by boiling or steam under pressure, is ready for use. The stability of the solution is not affected in the least by sterilization.

The chemical reactions involved in the preparation of this solution are probably as follows:



Four possibilities:

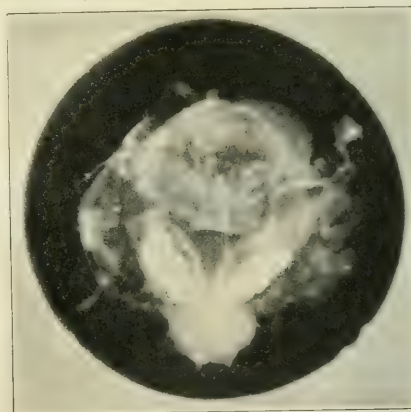
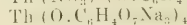
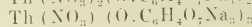
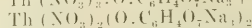
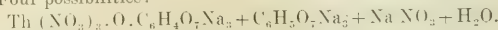


FIG. 2.—From a series of vesiculograms by Dr. E. M. Watson, Assistant Resident Urologist, James Buchanan Brady Urological Institute.

This solution contains approximately fifteen per cent of thorium nitrate, about nine per cent of sodium nitrate, and twenty-one per cent of sodium citrate, the thorium being most probably in the form of a double citrate of sodium and thorium, as shown above.

As the thorium content of the solution alone is responsible for its shadow-casting properties, its percentage strength has to be greater on account of the large size of the molecule of this double citrate than if the solution contained thorium nitrate alone, in which the molecules are much smaller and in consequence the atomic concentration much greater. The outline of the renal pelvis and ureter, as given by the shadow cast by this solution, is not only quite definite, but the shadow itself is of remarkably clear delineation.

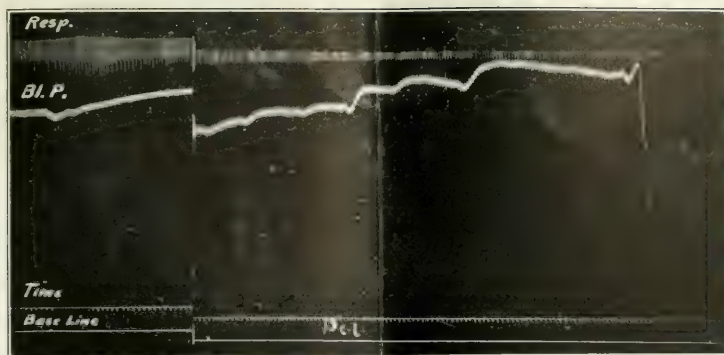


FIG. 3.—Kymographic tracings (Dog IX), showing rise in blood pressure, increase in pulse rate and decrease in respiration, after intravenous injection of 15 per cent thorium solution in small amounts -10 cc. The increase in magnitude of the respiratory waves in two places toward the end of the tracings is due to muscular twitching.

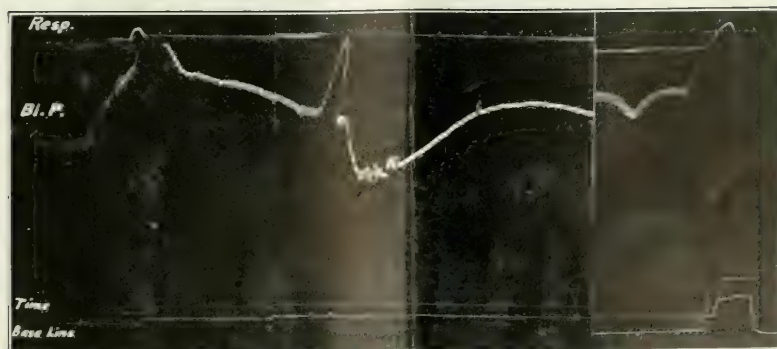


FIG. 4.—Kymographic tracings (Dog XIX), showing rise in blood pressure, increase in pulse rate, decrease in respiration, and periods of apnea, after small injections of 10 cc., or less, of 15 per cent thorium solution intravenously, both vagi having been cut before the injection was begun.

In addition to its great opacity to the X-ray, the solution, either by its adhesive properties, by its capability of being absorbed by calculi, or by means of its comparative density, accentuates the shadows of calculi in the urinary tract when they are not ordinarily seen in plain Roentgen ray plates.

The marked degree of fluidity of the solution is of great advantage, for it so rapidly escapes from the kidney pelvis, ureter and bladder, that a plate, made a few minutes after the injection has been discontinued, gives no suggestion of a shadow, thus showing that the solution has been completely eliminated from the urinary tract.

That the solution is not irritating to the mucous membranes of the bladder, ureters, and pelvis of the kidneys, has been demonstrated by the fact that no urinary symptoms have been observed in the cases in which it has been used. Subsequent cystoscopic examinations have shown no evidence whatsoever of any inflammation of the vesical mucous membrane; the examination of the bladder, ureters and kidney pelvis, in cases which have come to operation within a few hours or days after its use, have shown no evidence of any irritative action. In the animals into whose peritoneal cavities this solution has been introduced, there has been no sign of any peritonitis at autopsy, and all of the fluid has been absorbed in most instances. The careful neutralization of the solution has been emphasized previously, and it is due to this fact that no irritating action has been observed.

The solution, although exerting an inhibitory action on the growth of the ordinary bacteria, is not bactericidal. Moulds grow in it upon standing; therefore, it must be sterilized and kept sterile while being used.

A word may be said in regard to the introduction of the solution into the renal pelvis and ureter. This is done by the gravity method by means of a burette with a rubber-tubing connection and a properly fitting nozzle for the end of the ureteral catheter, the burette being held slightly above the level of the patient. This method is recognized by urologists at the present time as being the least dangerous and most successful for completely distending the renal pelvis. Injection by means of a syringe has fallen into disuse because of the great danger of over-distension of the pelvis, and the forcing of the solution into the renal parenchyma or into the peri-renal tissues. In practically all the cases of death reported as due to the use of collargol, this latter procedure was employed.

PHARMACOLOGIC ACTION OF THE SOLUTION.

The pharmacologic action of this solution has been studied experimentally in dogs, cats, rabbits and guinea-pigs: five animals having been used altogether. In these animals, small doses, given intravenously, intraperitoneally, intramuscularly and subcutaneously, produced no effect. Larger doses have in a few instances produced diarrhoea, while still larger doses have caused death preceded by muscular twitchings, clonic convulsions and coma. These fatal doses, of course, were far above the ordinary limits of clinical usage. In a few instances 2 cc. of this fifteen per cent solution per kilogram (intraperitoneally and intramuscularly) proved fatal in these animals, much larger doses being required intravenously to produce

death. Even these figures in the case of an ordinary man of 70 kg. would allow the use of 140 cc. of the solution, which would be ten times as great as that used in a simple pyelogram, and hundreds of times greater than any small amount that might be absorbed during the procedure. As a matter of fact, much larger amounts than this have been used in the renal pelvis without any ill effects.

The tolerance of these animals for the solution seemed to vary greatly with the method of administration; dogs, for instance, being much more tolerant of the solution intravenously than when it was given intraperitoneally. The reverse, however, was found to be true in the case of rabbits. Guinea-pigs tolerated the solution in much larger doses intraperitoneally than cats.

Outside the body the solution prevents the coagulation of the blood. When introduced into the circulation it causes no change in the cellular elements of the blood. The number of red and white blood cells and the hemoglobin content remain the same after its introduction.

In studying the effects of the intravenous injection of the solution, twelve dogs and two rabbits were used. In only one of these dogs did the solution prove acutely fatal, 5 cc. per kg. having caused death in five hours in Dog XXVII. One of the rabbits died three days after the injection and at autopsy marked parasitic infection was found, so that it is impossible to say whether the thorium solution was in any way responsible or not.

The intravenous injection of this fifteen per cent thorium solution, in dogs, in small amounts (10-15 cc.), causes first a rise in blood pressure with an increase in pulse rate, the respirations being also increased. All three quickly return to normal. However, if the small doses be repeated over a period of several hours, the animal being etherized by intratracheal insufflation, there will be a decrease in the depth of the respirations after each injection. These periods of decrease in respiration later become periods of apnoea, the respiration finally ceasing quite a while before the ventricular contractions stop. The ventricular contractions, as a rule, become quite irregular before they cease altogether. There is also a final drop in blood pressure, as would be expected. The cutting of the vagi has no effect upon these phenomena. By this method as much as 12 cc. per kg. (Dogs IX and XI) have been required to produce death. In a few of these dogs muscular twitchings followed by clonic convulsions were observed toward the end of the experiment (Figs. 3 and 4).

As much as 4 cc. per kg. (Dog XVIII) have been given at a single dose without any symptoms being observed, and with no effect on the phenolsulphonephthalein output or on the blood urea content. This animal was sacrificed on seventy days; the autopsy proved negative. There was no demonstrable change in kidney function, as indicated by these two methods of investigation, in any of the dogs to which from 1 to seven per cent thorium solution was administered intravenously (Figs. 5 and 6). In some of the dogs there was diuresis of short duration. In rabbits, 3 cc. per kg. of this fifteen per cent solution, when given in a single dose (Rabbit VIII), produced

immediate muscular twitching and clonic convulsions followed by rapid and complete recovery, no untoward effect being observed afterward. Autopsy in this instance was also negative. Two cc. per kg. (Rabbit VIII) caused death in three days. At autopsy a generalized parasitic infection was found.

The solution was injected into the peritoneal cavity of five dogs, three cats, seven rabbits, and three guinea-pigs. It caused death in one instance in each of the different animals.

Three and a half cc. of this fifteen per cent solution per kg. in Dog XXI produced slight diarrhoea; no other effects were observed. Three cc. per kg. (Dog XIX) caused a bloody

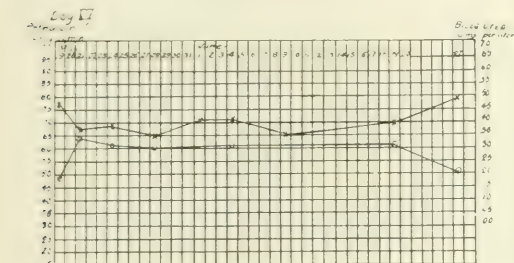


FIG. 5.—Chart of Dog VI, showing no change in phenolsulphonaphthalein output or blood urea content after injection of 1 cc. per kg. of 10 per cent thorium solution.

X = phenolsulphonaphthalein output for two hours and ten minutes.
o = blood urea, grams per liter.

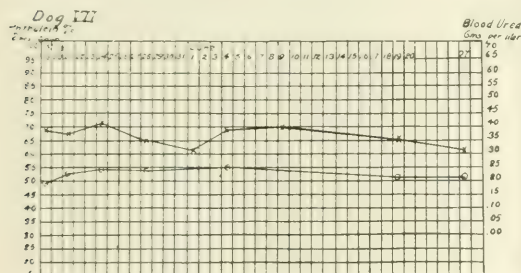


FIG. 6.—Chart of Dog VII, showing no change in phenolsulphonaphthalein output or blood urea content after intravenous injection of 1.5 cc. per kg. of 10 per cent thorium solution.

X = phenolsulphonaphthalein output for two hours and ten minutes.
o = blood urea, grams per liter.

diarrhoea for twenty-four hours following the injection, with prompt recovery; the animal was sacrificed in thirty-six days for a kymographic experiment. The autopsy showed central necrosis of the liver. All the other organs were normal. Two cc. per kg. (Dog VIII) proved fatal in eighteen hours after the injection. At autopsy this animal showed hemorrhagic gastroenteritis and congestion of all the organs. No fluid, however, was present in the peritoneal cavity and the peritoneal surfaces were smooth and glistening. Microscopically central necrosis of the liver was found. In cats, three cc. per kg. (Cat III) caused death in three days. This animal showed loss of appetite; it was dull and apathetic. At autopsy a small

amount of clear fluid was found in the peritoneal cavity; the peritoneal surfaces were normal. All the organs were normal in gross appearance. Microscopically cloudy swelling of the liver was seen. Two cc. per kg. (Cat IV) produced no effect. This animal was sacrificed in eighty-four days, the autopsy showing generalized parasitic infection. One cc. per kg. (Cat II) produced no effect. This animal was sacrificed in ninety-four days, the autopsy showing nothing abnormal. In rabbits 10 cc. per kg. (Rabbit VII) produced death, preceded by convulsions, in twelve hours. The autopsy showed a small amount of bloody fluid in the peritoneal cavity; the peritoneal surfaces were normal. Seven and a half cc. per kg. in Rabbit IX produced no effect. In guinea-pigs 8 cc. per kg. (Guinea-pig IV) caused death in forty-eight hours. Some clear fluid was found in the peritoneal cavity at autopsy; the peritoneal surfaces and organs were normal in appearance. Three cc. per kg. (Guinea-pig III) showed no effect.

Intramuscularly, small quantities distributed over different portions of the body were absorbed, no effect being produced. In dogs, 2 cc. per kg. given deeply into the lumbar muscles (Dog XXXI) caused death in three days. Hemorrhage and necrosis were observed at the site of the injection and at autopsy congestion of all organs was found. In cats, 4 cc. per kg. (Cat VI) caused death in twenty-four hours. The autopsy showed a slight hemorrhage at the site of the injection, and bloody fluid in the pleural and pericardial cavities; microscopically central and midzonal necroses of the liver were seen.

Subcutaneously, small doses were well absorbed, producing no effects whatever if well distributed over the body. In dogs, 2 cc. per kg. (Dog XIV, who four days previously had received 1 cc. per kg. intraperitoneally) were followed by death in forty-eight hours. Muscular twitchings were observed for twenty-four hours preceding death. The autopsy showed hemorrhage at the site of the injection; there was no free fluid in the peritoneal cavity; all the organs were congested. In cats, 4 cc. per kg. (Cat V), caused death in twelve hours. The autopsy showed acute congestion of the spleen, petechial hemorrhages in the heart muscle, and central and midzonal necroses of the liver.

MODIFICATIONS OF THE SOLUTION.

With the idea of a possible simplification of the solution, various attempts were made to modify it, but these modifications, when tested experimentally, have either shown an increase in toxicity, or have been responsible for the production of certain symptoms that are not observed when the original solution is used.

Since the thorium content of the solution is alone responsible for its shadow-casting properties, as noted above, it was thought that a solution containing only the double neutral citrate of sodium and thorium would be a great step towards simplification.⁵ This, however, in fifteen per cent concentration, proved

⁵ I am indebted to Dr. H. A. B. Dunning, of the firm of Hynson, Westcott & Co., of this city, for the preparation of this double neutral citrate and the modified solutions employed in these experiments.



FIG. 7.—Normal renal pelvis and ureter.



FIG. 10.—Accentuation of the shadow of a renal calculus by the thorium solution, a plain roentgenogram having shown no shadow.



FIG. 13.—Bilateral hydronephroses, and hydroureters, dilated and trabeculated bladder, dilated internal sphincter, due to congenital obstruction in posterior urethra.



FIG. 8.—Slightly irregular pelvis due to old chronic inflammatory process.

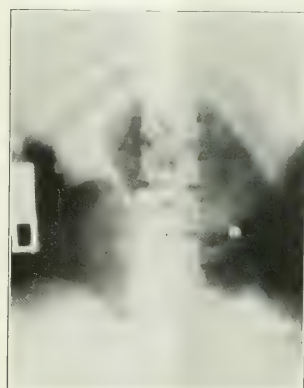


FIG. 11.—Moderate grade of hydronephrosis due to a calculus in the lower end of the left ureter.

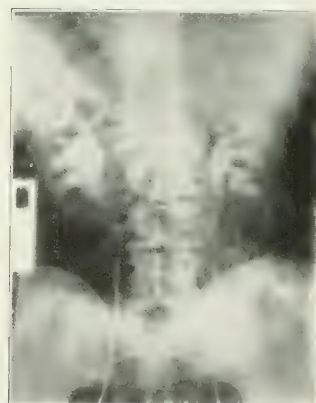


FIG. 14.—Double pyelogram showing a slight hydronephrosis in the lower portion of the pelvis of the left kidney.



FIG. 9.—Kink in upper ureter due to aberrant vessels to lower pole of kidney, with a slight grade of hydronephrosis.



FIG. 12.—Large hydronephrosis due to a congenital stricture of the ureter.



FIG. 15.—Double pyelogram, showing similar types of renal pelvis on both sides.

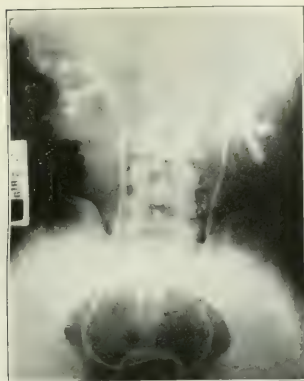


FIG. 16.—Double pyelogram showing a bifid pelvis on the left; kink in lower end of right ureter.



FIG. 19.—Plain roentgenogram of bladder showing indefinite shadow in the bladder region due to numerous small calculi.



FIG. 22.—Cystogram. Case of tabes dorsalis showing trabeculated bladder with diverticulum, dilatation of the internal sphincter and funnel-shaped posterior urethra.



FIG. 17.—Horseshoe kidney; case of Dr. Guy L. Hunner.



FIG. 20.—Cystogram (same case as Fig. 19), the bladder being filled with ten per cent thorium solution.



FIG. 23.—Congenital hydronephrosis in a boy 11 years of age.

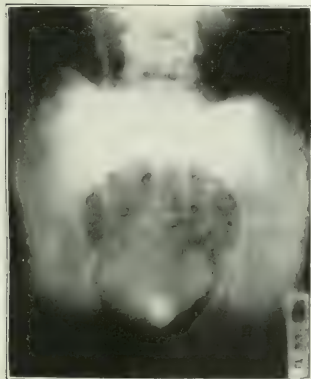


FIG. 18.—Cystogram showing trabeculated bladder with diverticulum, dilatation and kinking of right ureter.



FIG. 21.—Same case as in Figs. 19 and 20 after thorium solution had been allowed to flow out of the bladder, showing sponge-like shadow due to the differing degrees of opacity of the calculi and thorium solution.



FIG. 24.—Double pyelogram showing a double renal pelvis with a calculus in the upper pelvis and a bifurcated ureter on the left side.

quite toxic as is shown by the following experiments: An intravenous injection of 4 cc. per kg. (Dog XX) caused a bloody diarrhoea for twenty-four hours, beginning six hours after the injection, the diarrhoea ceasing by the beginning of the third day. The dog was dull and apathetic, and had no desire for food. Death occurred in seventy-two hours. The chief autopsy finding was central necrosis of the liver with congestion of the kidneys. Three cubic centimeters intravenously (Dog XVI) caused a marked diarrhoea for forty-eight hours following the injection, during which time the dog was very sick and stupid. This animal showed marked loss of appetite and weight. The total phenolsulphonephthalein output for two hours and ten minutes dropped from 88 per cent at the time of injection to 50 per cent on the thirty-fourth day, at which time the animal was sacrificed. At autopsy no unusual findings were observed grossly. Unfortunately, the sections were lost.

These experiments show that a solution containing the double neutral citrate alone could not be used. Sollman and Brown^{*} investigated the pharmacologic action of the double citrate of sodium and thorium; these authors found that one gram per kg. given intravenously caused death immediately and that 5 gm. per kg. caused death after twenty-four hours. The results of the studies of these authors agree with mine, excepting in the autopsy findings. They report ulceration of the buccal mucous membrane and deposits of calcium in the organs; no such changes were found after the use of various doses of any of the thorium solutions that I have investigated. These authors furthermore state that the toxic effects of the double citrate may be largely accounted for by the sodium citrate content, for their experiments with sodium citrate alone gave practically the same results.

A solution made in the same way as the original solution, but in which thorium chloride was used in place of thorium nitrate in its preparation, caused diarrhoea for twenty-four hours in Dogs XXIII and XXVI. In each instance 4 cc. per kg. were given intravenously. These animals were sacrificed in forty-four and thirty-seven days, respectively, and the autopsies in both instances were negative.

A solution containing the double neutral citrate of sodium and thorium, fifteen per cent, and ten per cent of sodium citrate, caused immediate death in Dog XXIV, after 2.5 cc. per kg. had been given intravenously. The autopsy was negative. In Dog XXVIII, 4 cc. per kg., intravenously, caused death in eighteen days. For twenty-four hours following the injection there was marked muscular twitching and diarrhoea. However, there was prompt recovery from these symptoms, but the gradual loss of weight and appetite continued until death ensued. The autopsy findings in this instance were negative.

A solution containing fifteen per cent of the double neutral citrate of sodium and thorium and ten per cent each of sodium chloride and sodium citrate caused death in sixteen days after the intravenous injection of 4 cc. per kg. (Dog XXV). This dog was apparently well until three days before death, when he began having convulsions and was very dull and apathetic.

^{*} Sollman & Brown: "Pharmacologic Investigations on Thorium." Amer. Journ. Physiology, 1907, XVIII, 426-456.)

Dog XXIX died at the end of an intravenous injection of 3 cc. per kg., the respirations ceasing before the ventricular contraction. The autopsy showed congestion of all the organs. Dog XXX, given 4 cc. per kg. intravenously, had diarrhoea for twenty-four hours with prompt recovery; there were no other symptoms. This animal was sacrificed in thirty days. The autopsy findings were negative.

From these observations, it is seen that the withdrawal of any of the component parts of the original solution would be harmful. The substitution of the chloride for the nitrate of thorium in the original solution produced diarrhoea.

CLINICAL USES.

Since the introduction of this solution into the Urological Clinic of this hospital eight months ago, it has been used in one hundred and twenty-five cases without any untoward effects whatsoever having been observed.

From the table of eighty-seven pyelograms (pp. 162-163) it will be seen that there were nausea and vomiting following its use in four cases. These symptoms could be readily accounted for by the ureteral catheterization alone, for they occur fully as frequently in cases where this alone has been done and no injection has been made into the renal pelvis or ureter. In one of these cases, on account of the irritability of the bladder, the patient had to be etherized before ureteral catheterization could be attempted; the etherization could account for the nausea and vomiting in this case. In the table of cystograms it is seen that nausea and vomiting occurred in one case, and slight nausea and frequency of urination in another. In the first case the nausea and vomiting occurred some hours after the cystogram had been made and was due in all probability to some indiscretion in diet. In the second case the patient was quite nervous, this condition possibly being entirely responsible for the symptoms.

The largest amount used in the entire urinary tract in a single case was 600 cc. of a ten per cent solution introduced into the bladder, ureters and renal pelves of a boy twelve years of age. The roentgenogram (Fig. 13) in this instance showed a dilated and trabeculated bladder with dilatation of the internal sphincter, double hydroureters and hydronephroses, due to a congenital obstruction in the posterior urethra. This patient showed no change in the phenolsulphonephthalein output or blood urea content; nor has there been any interference with kidney function demonstrated in any of the cases. For pyelograms, from 5 to 150 cc. of a fifteen per cent solution have been used, and for cystograms from 30 to 930 cc. of a ten per cent solution.

CONCLUSIONS.

1. Thorium solution fulfils all the conditions necessary for an ideal pyelographic medium.
2. Clinically, there has never been the slightest evidence of toxicity in a series of one hundred and twenty-five cases, the amounts used in a single case varying from a few cubic centimeters to almost a litre. This alone is proof of its non-toxicity.
3. Experimentally, although in a few instances death has followed the injection of large doses into the peritoneal cavity

TABLE OF PYELOGRAMS. FIFTEEN PER CENT THORIUM SOLUTION.

Photo No.	History No.	Name	Diagnosis	Pyelogram	Amount of contrast medium injected	Symptoms following injection	Phenolsulphonphthalein output before injection	Phenolsulphonphthalein output after injection	Remarks
1	247 4466 G. C.	49	Ureteral calculus	Pyelogram (S)	None	None	41%, half hour.		
2	247 4474 J. T.	48	Pyelitis—left	Pyelogram (S)	None	None	50%, half hour.		
3	247 4481 D. M.	48	Hydronephrosis	Pyelogram (S)	None	None	Half hour, 14%, R.;		Right nephrectomy.
4	247 4482 H. C.	49	Hydronephrosis	Pyelogram (S)	None	None	30% L.		
5	247 4519 P. C. H.	49	Renal tuberculosis	Pyelogram (S)	None	None	Half hour, 10%, R.; Total, 62%		Pyelitis, right.
6	247 4520 H. C.	49	Renal tuberculosis	Pyelogram (S)	None	None	3% L.		Right nephrectomy.
7	247 4521 H. C.	49	Hydronephrosis	Pyelogram (D)	L-13 cc.	None	Total, 56% Total, 67%		Plastic operation on pelvis of left kidney.
8	247 4524 F. W. H.	49	Renal calculus	Pyelogram (S)	None	None	Half hour, 15% L. Total, 55%		Right pyelotomy.
9	247 4525 M. Y.	49	Cholelithiasis	Pyelogram (S)	None	None	Half hour, 26% R. Total, 56%		
10	247 4527 R. Me.	49	Hemorrhagic nephritis	Pyelogram (D)	R-25 cc. L-12 cc.	None	Half hour, 61% Total, 88% R: 12% L: Trace		Tonsillithomy. Lavage of renal pelvis with AgNO ₃ . Injection of horse serum.
11	247 4528 W. S.	49	Pyelonephritis	Pyelogram (S)	None	None	Half hour, 17% Total, 61%		
12	247 4529 F. S. M.	49	Pyelonephritis	Pyelogram (D)	None	None	R: Trace. L: Half hour, 18% R.		Lavage of renal pelvis with AgNO ₃ solution.
13	247 4530 T. L. C.	49	Pyelitis	Pyelogram (D)	None	Sl. nausea and vomiting.	Half hour, 18% R.; 5% L. Trans-verse, 25%.		Lavage of renal pelvis with AgNO ₃ solution.
14	247 4531 T. J. W.	49	Prostatic hypertrophy	Pyelogram (D)	None	None	Half hour, 14% R.; Total, 60%.		
15	247 4532 J. J. Metz	49	Hydronephrosis	Pyelogram (S)	None	None	Half hour, 34% R. 21% L. 10% L.		
16	247 4533 P. H.	49	Hydronephrosis	Pyelogram (D)	None	Sl. nausea and vomiting.	Total, 25% Blood Total, 26% urea, 0.75 gms. Bl. urea, 0.6 gms.		Etherization for cystoscopy. Suprapubic cystostomy with division of ureteral septum.
17	247 4534 F. N.	49	Essential hematuria	Pyelogram (D)	R-7 cc. L-3 cc.	None	Total, 61%		Lavage of renal pelvis with AgNO ₃ solution.
18	247 4535 J. B.	49	Prostatic hypertrophy. Vesicopyelogram (S)	16 cc.	None	Total, 59%	Total, 59%		Perineal prostatectomy and lithotomy.
19	247 4536 W. L. C.	49	Prostatic hypertrophy. Pyelopyelogram (S)	16 cc.	None	Total, 49%	Total, 49%		Lavage of renal pelvis with AgNO ₃ solution.
20	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Total, 60%	Total, 60%		Left nephrectomy.
21	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Total, 60%	Total, 62%		Left nephrectomy.
22	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	None	None	Total, 60%	Total, 62%		Left nephrectomy.
23	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Total, 2%	Bl. urea, 1.4 gms.		Ureterolithotomy.
24	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Bl. urea, 1.6 gms.			Ureterolithotomy.
25	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Total, 63%	Total, 63%		Etherization for cystoscopy.
26	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	L-25 cc.	None	Total, 53%	Total, 53%		Pyelotomy.
27	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	L-25 cc.	None	Half hour, 14% R.; Total, 52%			
28	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (S)	None	None	Half hour, 22% R.; Total, 63%			Left nephrectomy.
29	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
30	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
31	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
32	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
33	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
34	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
35	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
36	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
37	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
38	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
39	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
40	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
41	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
42	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
43	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
44	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
45	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
46	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
47	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
48	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
49	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
50	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
51	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
52	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
53	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
54	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
55	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
56	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
57	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
58	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
59	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
60	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
61	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
62	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
63	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
64	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
65	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
66	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
67	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
68	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
69	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
70	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
71	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
72	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
73	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
74	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
75	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
76	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
77	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
78	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
79	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
80	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
81	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
82	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
83	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
84	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
85	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
86	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
87	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
88	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
89	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
90	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
91	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
92	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
93	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
94	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
95	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
96	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
97	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
98	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
99	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			
100	247 4439 J. W.	31	Ureteral calculus. Pyelopyelogram (D)	R-14 cc. L-14 cc.	None	Half hour, 21% R.; Total, 59%.			

TABLE OF PYELOGRAMS. FIFTEEN PER CENT THORIUM SOLUTION—*Cont'd.*

No.	Plate No.	History No.	Name.	Age.	Diagnosis.	Pyelogram.	Quantity of the removed secretion.	Symptoms following injection.	Plenulphosphophyllen output before injection.	Plenulphosphophyllen output after injection.	Remarks.
56	371	4719	L. C. H.	27	Renal tuberculosis	Pyelogram (S)	R 80 cc.	None	Half hour, 20% R; Total, 52% L.		Right nephrectomy.
57	377	5746	P. H.	29	Pnephrosis	Pyelogram (S)		None	Half hour, 0% R; Total, 68% L.		Right nephrectomy.
58	382	4772	C. C.	37	Renal tuberculosis	Pyelogram (S)		None	Half hour, 32% R; Total, 68% L.		Left nephrectomy.
59	381	1806	S. K.	32	Ureteral calculus	Pyelogram (S)	R 100 cc.	None	Half hour, 30% R; Total, 62% L.		Left pyelotomy.
60	387	1777	B. O. B.	35	Renal calculi	Pyelogram (S)		None	Half hour, 35% R; Total, 68% L.		Lavage of renal pelvis with AgNO ₃ solution.
61	405	4803	H. K.	27	Pyelitis (rt)	Pyelogram (S)	R 80 cc.	None	Half hour, 35% R; Total, 68% L.		Lavage of renal pelvis with AgNO ₃ solution.
62	410	4763	H. K.	25	Pyelitis (rt)	Pyelogram (S)	R 70 cc.	None	Half hour, 35% R; Total, 68% L.		Lavage of renal pelvis with AgNO ₃ solution.
63	396	4808	C. H. R.	42	Ureteral calculus (rt)	Pyelogram (S)		None			Ureterostomy.
64	401	1808	C. H. R.	42	Ureteral calculus (rt)	Pyelogram (S)		None			Ureterostomy.
65	394	4801	F. W. G.	41	Prostatitis and seminal vesiculitis	Injection of seminal vesicles.		None			Ureterostomy.
66	405	4824	W. M. P.	29	Nephralgia	Pyelogram (S)		None			
67	407	4816	W. L. Metc.	56	Renal calculi. Double renal pelvis and ureter.	Pyelogram (D)	R 75 cc.	None	Total, 54% L.		
68	408	4841	A. S. H.	39	Chr. prostatitis	Pyelogram (D)		None			
69	429	4838	R. K. H.	38	Nephralgia	Pyelogram (S)		None	Half hour, 22% R; Total, 49% L.		
70	424	4840	H. W. F.	32	Chr. prostatitis. Verumontanitis.	Pyelogram (S)	R 80 cc.	None	Total, 49% L.		
71	429	4854	F. H.	33	Median bar hypertrophy	Pyelogram (S)		SI nausea	Half hour, 18% R; Total, 96% L.		Partial operation.
72	431	3189	C. P. F.	25	Median bar hypertrophy	Pyelogram (D)		None	Half hour, 15% R; Total, 25% L.		Partial operation.
73	437	4867	C. J.	61	Prostatic hypertrophy	Pyelogram (S)	R 110 cc.	None			
74	445	4906	W. H. K.	54	Chr. prostatitis	Pyelogram (D)	R 90 cc.	None	Half hour, 15% R; Total, 46% L.		
75	443	4892	H. M. S.	40	Chr. cystitis. Prostatic hypertrophy. Median bar	Pyelogram (S)	R 100 cc.	None	Half hour, 22% R; Total, 55% L.		
76	447	4916	J. G.	39	Essential hematuria	Pyelogram (D)	R 30 cc.	None	Half hour, 0% R; Total, 35% L.		
77	460	4916	J. G.	39	Essential hematuria	Pyelogram (D)	R 20 cc.	None	Half hour, 7% R; Total, 48% L.		
78	448	4928	B. G.	32	Perinephric abscess (rt)	Pyelogram (S)	R 100 cc.	None	Total, 72% L.		Incision and drainage of perinephric abscess.
79	452	4922	F. M. B.	31	Generalized pychitis	Pyelogram (D)		None			Lavage of pelvis with AgNO ₃ solution.
80	455		P. M.	39	Chr. Cystitis and Chr. Prostatitis	Pyelogram (D)		None			
81	462	5002	J. N.	39	Double pyelitis	Pyelogram (D)	R 100 cc.	None	Half hour, 14% R; Total, 54% L.		Lavage of pelvis with AgNO ₃ solution.
82	465	4901	C. F. P.	39	Renal tuberculosis	Pyelogram (S)		None	Half hour, 5% R; Total, 54% L.		Right nephrectomy.
83	463	4976	R. H.	33	Essential hematuria	Pyelogram (S)		None	Half hour, 20% R; Total, 88% L.		Lavage of renal pelvis with AgNO ₃ solution and irrigation of oses.
84	468	4976	R. H.	33	Essential hematuria	Pyelogram (S)		None	Half hour, 20% R; Total, 88% L.		Lavage of renal pelvis with AgNO ₃ solution and irrigation of oses.
85	470	4982	C. S.	28	Double pyelitis	Pyelogram (D)	R 100 cc.	None	Half hour, 17% R; Total, 46% L.		Lavage of renal pelvis with AgNO ₃ solution.
86	472	4985	D. C. B.	38	Pyelitis (rt)	Pyelogram (D)	R 100 cc.	None	Half hour, 17% R; Total, 46% L.		Lavage of renal pelvis with AgNO ₃ solution.
87	476	4992	H. K. B.	29	Renal tuberculosis bilateral	Pyelogram (S)		None	Half hour, 28% R; Total, 42% L.		

S = Single, D = Double, R = Right kidney, L = Left kidney, Tr = Traces, Traces = Traces of phenol (phenolphthalein) output, Total = Phenol (phenolphthalein) output for two hours and ten minutes.

TABLE OF CYSTOGRAMS. TEN PER CENT THORIUM SOLUTIONS.

No.	Plate No.	History No.	Name.	Age.	Diagnosis.	Cystogram.	Quantity of chromosomal material.	Symptoms before injection.
1	185	333	S. V.	...	Chr. prostatitis.	Cystogram...	...	None.
2	213	413	W. Z.	...	Tuberc. testis.	Cystogram...	...	None.
3	214	4125	G. C. T.	56	Prostatic hypertrophy.	Cystogram...	...	None.
4	224	4438	D. S. B.	32	1st. of bladder, cystitis, contracted bladder.	Cystogram...	...	None.
5	226	4434	P. H.	45	Tubes dorsalis.	Cystogram...	...	None.
6	241	4426	M. K.	38	Prostatic hypertrophy.	Cystogram...	...	None.
7	249	4474	J. B. C.	49	Prostatic hypertrophy, cerebro-spinal lues.	Cystogram...	...	None.
8	255	4449	P. H.	62	Carcinoma of bladder.	Cystogram...	...	None.
9	256	4443	H. H.	...	Tuberc. of prostate hyp.	Cystogram...	...	None.
10	259	3376	W. C.	59	Cerebro spinal lues.	Cystogram...	...	None.
11	262	4389	B. G.	31	Cystitis, Leukoplakia.	Cystogram...	...	None.
12	274	4441	J. M.	24	Hydronephrosis.	Cystogram...	...	None.
13	3391	4618	J. G.	62	Tubes dorsalis.	Cystogram...	...	None.
14	298	4523	M. S.	55	Cerebro-spinal lues.	Cystogram...	...	None.
15	316	4573	F. H.	44	Cerebro spinal lues.	Cystogram...	...	None.
16	319	4591	T. F.	60	Prostatic hypertrophy.	Cystogram...	...	None.
17	337	4641	J. J. W.	47	Prostatic hypertrophy.	Cystogram...	...	None.
18	355	4716	E. W.	37	Tuberc. vesiculi.	Cystogram...	...	None.
19	362	4717	A. W.	42	Tubes.	Cystogram...	...	None.
20	364	4728	D. C. O.	28	Cerebrospinal lues.	Cystogram...	...	None.
21	374	4753	S. P. E.	37	Prostatic hypertrophy.	Cystogram...	...	None.
22	409	4514	R. L.	51	Retro-vesical sarcoma.	Cystogram...	...	None.
23	413	4592	A. B.	43	Tuberc. of prostate, prostatic nephrosis (right).	Cystogram...	...	None.
24	411	4688	K. E. K.	45	Median Bar hypertrophy.	Cystogram...	...	None.
25	415	4824	C. M. S.	55	Carcinoma of prostate.	Cystogram...	...	None.
26	434	4885	S. R. D.	44	Hypertrophy of trigone.	Cystogram...	...	None.
27	444	4881	H. F.	48	Hydronephrosis.	Cystogram...	...	None.
28	459	4601	W. B. K.	60	Prostatic hypertrophy.	Cystogram...	...	None.
29	453	4727	A. B.	47	Prostatic hypertrophy.	Cystogram...	...	None.

and tissues of animals, larger doses intraperitoneally and intravenously have produced no ill effects.

4. That the solution is non-irritating is shown by the absence of urinary symptoms after its use, and the absolute lack of any such evidence cystoscopically, and at operation.

5. The pyelograms and cystograms made with this solution show a splendid shadow which possesses an unusual clearness of delineation.

6. The solution is clear and watery; therefore it possesses a great degree of fluidity, permitting its ready elimination from the urinary tract.

7. It is perfectly clean and does not stain the linen. In this particular it possesses another marked advantage over other solutions, particularly those of the silver salts.

8. It is quite inexpensive, being about one-third as costly as collargol.

I desire to express my sincere thanks to Dr. Hugh H. Young, Director of the James Buchanan Brady Urological Institute, for his constant and enthusiastic interest throughout the course of this work; to Dr. C. A. Waters, of the Department of Roentgenology, for his invaluable assistance in the roentgenographic work; to Dr. E. K. Marshall, of the Department of Pharmacology, and to Dr. George Pierce, chemist of the James Bu-

chanan Brady Urological Institute, for their helpful suggestions; to Dr. Montrose T. Burrows, of the Department of Pathology, for his kind assistance in reviewing the pathological material; and to Dr. W. S. Gorton, physicist of the James Buchanan Brady Urological Institute.

DISCUSSION.

DR. HUNNER: We ought to congratulate Dr. Burns on this very important contribution for those who work in urology. In working in a special line, as I have been doing for some time; viz., on ureter stricture, I have regretted often not having X-ray pictures of the condition of the dilated pelvis and the dilated ureter above the point of stricture. I have not felt justified in using the older solutions, such as collargol, because of the actual danger to the patient, and because in those particular cases it was not going to do the patient any good. A diagnosis could be made with the means at hand and it did not seem justifiable to go further. Now, from the experience I have had with thorium solution, I feel that we are perfectly justified in going further and getting an actual picture as a matter of record and to demonstrate to others the condition, without any added risk to the patient. I have always felt we were not justified in using collargol except in rare instances where perhaps there was doubt as to whether we were dealing with a tumor of the kidney, or in some such case where we actually needed an X-ray picture. The thorium method described by Dr. Burns this evening will be of great value in many cases.

A STATISTICAL STUDY OF 635 LABORS WITH THE OCCIPUT POSTERIOR.

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INTRODUCTION.

The recent American literature on the subject of obliquely posterior positions of the occiput has indicated such a widespread belief in the unfavorableness of this common occurrence, and such radical opinions with regard to the proper methods of treatment, that this study was undertaken for the purpose of learning from our clinical experience whether there is any justifiable basis for such views. We have always viewed these cases with perfect equanimity and have been impressed with their benignity, but so far without any definite statistical evidence of our own in favor of such a view. The occiput obliquely posterior presentations have always been a stumbling block for physicians, and only somewhat recently have the conservative obstetricians come to the conclusion that they are little, if any, worse than the anterior varieties. However, this view seems not to be universal, for, only within the past year, an American author has advocated Cæsarean section in certain cases of this class, even in the absence of any other indication, and the majority of writers refer repeatedly to the marked difficulties encountered in these cases.

The following points have been studied and will be considered in order: Frequency, internal rotation, time of rupture of the membranes, character of the delivery, necessary operative measures, indications for operations, infant mor-

tality, duration of labor, type of pelvis, size of the child, and maternal morbidity and mortality. The first portion of the article is devoted to the presentation of the statistical findings; in the second portion the historical aspects are considered and a short discussion of the various findings is attempted.

STATISTICAL FINDINGS.

Material.—The histories of the first 1500 patients admitted to the Obstetrical Ward of the Johns Hopkins Hospital up to November, 1915, were examined and a note was made of the position of the child, as determined by abdominal palpation and by vaginal touch. The latter was always given preference over the former as being more accurate, but where no vaginal examinations were made the findings on palpation were considered final. Of the total number of admissions, 1730 were not available for our study. This group includes patients that were classified as "not pregnant," "not delivered," "admitted post partum," etc., as well as those in whom no definite diagnosis was made, usually because the patient was admitted very late in labor. Accordingly, 5770 cases, representing 5801 children, were available for analysis, and the following table shows the frequency with which the various presentations were noted:

TABLE 1.—FREQUENCY OF THE VARIOUS PRESENTATIONS.

	Number.	Percentage.
Vertex	5488	94.60
Face	20	.34
Brow	7	.13
Breech	226	3.87
Transverse	56	.96
Compound	4	.07
	5801 *	99.97

* Thirty-one cases of twin pregnancy are included.

Table 2 shows the incidence of the various varieties in the 5488 vertex presentations.

TABLE 2. INCIDENCE OF VARIETIES OF VERTEX PRESENTATIONS.

Position.	Number.	Percentage.
L. O. A.	2613	47.61
R. O. A.	1046	19.06
L. O. T.	706	12.86
R. O. T.	488	8.89
L. O. P.	181	3.30
R. O. P.	437	7.96
O. P.	17	.31

Frequency.—From Table 2 it is seen that there were 635 cases of occiput posterior among 5488 vertex presentations, an incidence of 11.57 per cent. The division into right and left varieties is also indicated. These figures are considerably lower than those usually given. The discrepancy is probably explained by the fact that the majority of the patients applied for admission only when labor was well advanced, and after a certain amount of internal rotation had taken place.

Except in the cases complicated by contracted pelvis, in which the head usually engages with the sagittal suture transverse, it is probable that a large proportion of the cases, registered as L. O. T. and R. O. T., originated as obliquely posterior positions. The only objection to such an assumption is the greater incidence of the former in our series, which would indicate that almost as many cases had originated in L. O. P. as in R. O. P., which is contrary to the general experience. Consequently, it has seemed advisable to limit our consideration to the cases in which a positive diagnosis of an actual posterior position had been made.

Internal Rotation.—A study of our histories gives the following information concerning this cardinal movement in the mechanism of labor:

TABLE 3.—CHARACTER OF INTERNAL ROTATION (SPONTANEOUS AND OPERATIVE).

	Spont.	Oper.	Total
Rotation through 135° to symphysis (O. A.) ..	419	77	496
Rotation through 45° to hollow of sacrum (O. P.)	70	19	89
	489	87	576
No rotation permitted (version or Cæsarean section)			46
No note on direction of rotation			7
No rotation (born in oblique diameter)			6
			635

With regard to the question of internal rotation, interest settles on the cases of spontaneous rotation as giving an index of the normal incidence. This was observed in 487 cases, and in 419 or 85.8 per cent the occiput turned toward the symphysis, while in the remaining 70 or 14.2 per cent the occiput was toward the sacrum.

A certain amount of information was gathered with regard to the influence of the factors that are usually brought forward to explain rotation.

In 22 cases it was noted in the histories that the head was "poorly flexed." Of these, 11 rotated spontaneously, 7 to O. A. and 4 to O. P. This finding substantiates the observation long since made that poor flexion interferes with rotation of any kind and tends to cause posterior rotation in a certain number of cases.

Of the 70 cases in which spontaneous posterior rotation was observed, 35, or 50 per cent, occurred in primiparæ (women who had never given birth to a viable child). As the number of primiparæ in the entire series was 316, or 19.16 per cent, it is apparent that the parity of the patient, and consequently the multiparous condition of the pelvic floor, cannot be held accountable for posterior rotation.

A factor which seemed to bear a causal relation to rotation of the occiput into the hollow of the sacrum was discovered in studying the direction of rotation in the various types of contracted pelvises.

TABLE 4.—DIRECTION AND METHOD OF ROTATION IN CASES WITH CONTRACTED PELVIS.

Type of pelvis.	Rotated to symphysis. (O. A.)		Rotated to hollow of sacrum. (O. P.)	
	Spont.	Oper.	Spont.	Oper.
	No.	%	No.	%
Generally contracted	49	81.6	8	13.3
Simple flat	7	77.7	1	11.1
Rachitic	10	71.4	3	21.4
Typical funnel	15	44.1	10	29.4
Generally contracted and flat funnel	6	54.5	4	36.3

From this table, considering spontaneous rotation alone, it is seen that in the usual types of contracted pelvis, the occiput rarely rotates posteriorly. In the group of cases marked by inlet contraction alone (generally contracted, simple flat and rachitic), rotation was noted in 83 cases, and in 70 of these it occurred spontaneously. Of these 70, in only 4, or 5.71 per cent, did the occiput rotate posteriorly; whereas in the 23 cases of typical funnel pelvis, in which spontaneous rotation occurred, it turned toward the sacrum in 8 cases, a percentage of 34.7. When the outlet contraction was complicated by a contraction at the brim (generally contracted and flat funnel), one case out of 7, or 14.3 per cent, showed posterior rotation. From the table it is very evident that funnel pelvis, in addition to predisposing toward rotation into the hollow of the sacrum, have a marked tendency to interfere

and rotation in any direction, and consequently the incidence of operative rotation is considerably increased. In the group of inlet contractions, out of 83 cases operative rotation was necessary in 13, or 15.6 per cent, while in 15 cases of typical funnel pelvis it was necessary in 15, or 33.3 per cent.

That this is more than a coincidence is indicated by the findings for the normal pelvis. Here there are two divisions, separated at the period when outlet mensuration became a routine procedure. In the former, outlet contractions were usually overlooked, while in the latter they were recognized and placed in a separate category.

TABLE 5. ROTATION IN NORMAL PELVES.

	Before outlet mensuration was instituted				After routine outlet mensuration was instituted			
	Rotated through 135° to the symphysis		Rotated through 45° to the hollow of the sacrum		Rotated through 135° to the symphysis		Rotated through 45° to the hollow of the sacrum	
	Spont.	Oper.	Spont.	Oper.	Spont.	Oper.	Spont.	Oper.
	N.	No.	N.	No.	N.	No.	N.	No.
Before outlet mensuration was instituted	114	68.6	26	15.6	24	14.4	2	1.2
After routine outlet mensuration was instituted	217	77.2	25	8.9	32	11.3	7	2.5

From Table 5 it appears that, in the former period when funnel pelvis were not recognized, there was a smaller percentage of spontaneous anterior rotations and a larger percentage of operative rotations than in the second group, in which funnel pelvis were recognized and classified as such. Considering spontaneous rotation alone, it is seen that, in the first group, consisting of 138 cases, posterior rotation occurred in 24, or 17.4 per cent, whereas in the second group, consisting of 249 cases, this outcome was noted only 32 times, or 12.9 per cent.

These observations on the effect of pelvic contraction upon internal rotation would indicate that resistance at the superior strait favors anterior rotation, but resistance at the inferior strait tends to rotate the occiput into the hollow of the sacrum and to increase the necessity for operative rotation.

The observations made upon rotation in premature and mature fetuses emphasizes the well-known fact that children with small heads tend to rotate posteriorly. Of the 71 cases in which the children weighed less than 2500 gm., rotation was observed in 58; in 10 there was no rotation, in 48 cases rotation, or version was noted, and in 3 no note was made as to the direction of rotation. Of these 58 cases, in 19, or 32.7 per cent, the occiput rotated posteriorly, and in 39, or 67.3 per cent, anteriorly. This makes the occurrence of the former nearly three times as frequent in premature as in mature children.

It is thus seen that faulty flexion of the head, funnel pelvis, and the small size of the child are three factors that through posterior rotation and that contraction at the superior strait prevents such rotation.

Rupture of the Membranes.—In each case the time of rupture of the membranes was noted, together with the size of the fetus when rupture occurred. In 33 cases these data were

not given and could not be inferred from the histories. In 28 additional cases the membranes were artificially ruptured early in labor, at the time of operation, and before there had been any reasonable chance of their spontaneous rupture. Excluding these two groups, there remained 574 cases in which there were satisfactory data concerning the time at which the membranes ruptured.

It was found that in 149 cases, or 18.2 per cent, the membranes had remained intact until the cervix was more than half dilated (5.0 cm.), whereas premature rupture had occurred in 125 cases, or 21.8 per cent. (It was thought that the term "premature rupture" might well be limited to rupture before half dilatation of the cervix, inasmuch as rupture of the membranes after the cervix is that size is rarely a complication of any moment.) Furthermore, it is interesting to note that in 179 cases, or 31.2 per cent, artificial rupture was resorted to after full dilatation.

In order to determine whether contraction of the pelvic inlet had any additional effect upon the incidence of this accident, the 121 cases associated with contracted pelvis were analyzed, and 101 cases were found in which data were available. Of these, in 25, or 24.7 per cent, spontaneous early rupture occurred. It is somewhat surprising that the difference is not more marked.

Character of Delivery.—Spontaneous delivery occurred in 489 cases, or 77.1 per cent of the entire series. In reviewing the movement of internal rotation in these cases the following facts were discovered:

TABLE 6.—ROTATION IN THE CASES OF SPONTANEOUS DELIVERY.

Rotated through 135° to the symphysis	414
Rotated through 45° to the hollow of the sacrum	62
Rotation not noted	8
No rotation—born in the oblique diameter	5
	489

By reference to Table 5, in which the direction of the rotation in all the cases is noted, it will be observed that spontaneous rotation through 135° to the symphysis occurred in 414 cases; and from the table above it is found that in 414, or 98.8 per cent of these, spontaneous labors occurred, whereas, among the 70 cases with spontaneous rotation into the hollow of the sacrum, 62, or 88.6 per cent, of the women were delivered without assistance. Thus it is evident that, when the usual anterior rotation occurs spontaneously, there is a minimal chance that artificial delivery will be indicated, whereas the anomalous spontaneous rotation into the hollow of the sacrum is followed by the need for interference in about 10 per cent of the cases, or ten times as frequently as in the usual anterior rotation. In spite of this, rotation into the hollow of the sacrum is not so serious a complication as is generally thought, because 10 per cent is comparatively a very low operative incidence.

Operative delivery was required in 146 cases, or 22.9 per cent. The following operations were performed:

TABLE 7.—LIST OF OPERATIVE PROCEDURES.

Version and extraction.....	39
Cæsarean section (abdominal)	7
Forceps.	
Rotation to symphysis (O. A.)	
Scanzonian (double application).....	high 6 mid 6 low 1
Single application—occiput still posterior (R. O. P. and L. O. P.).	high 0 mid 4 low 0
After complete spontaneous anterior rotation (O. A.)..	high 0 mid 0 low 5
After spontaneous rotation to an obliquely anterior position (L. O. A. and R. O. A.).	high 1 mid 1 low 14
After spontaneous rotation to a transverse position (L. O. T. and R. O. T.).	high 1 mid 10 low 1
After manual rotation to an obliquely anterior posi- tion (L. O. A. and R. O. A.).	high 1 mid 1 low 4
After manual rotation to a transverse position (L. O. T. and R. O. T.).	high 8 mid 10 low 8
Rotation to hollow of sacrum (O. P.).	
After complete spontaneous rotation into the hollow of the sacrum.	high 0 mid 1 low 7
After accidental instrumental rotation into the hol- low of the sacrum.	high 0 mid 3 low 0
After intentional rotation into the hollow of the sacrum.	high 0 mid 3 low 3
Incomplete rotation.	
Accidentally delivered in R. O. T. from an original R. O. P.	low 1

The various accessory operations, such as manual dilatation, vaginal hysterotomy and induction of labor, have been disregarded.

The number of patients delivered by the various types of forceps operation is of interest as showing the course of development of our present treatment. When the clinic first opened, the Scanzonian operation was usually performed when rotation had not occurred spontaneously, but after a short period the method of manual rotation followed by a single application of forceps was given a trial and proved so successful that it is now the usual method of treatment. In the latter half of the series there were only two cases of double application, the procedure being reserved for the rare cases in which manual rotation is impossible. In the course of my five years' association with the service I have never even seen the operation performed. An account of our present methods of treatment will be presented in the latter part of this article.

Indications for Delivery.—The following table gives the indications for operative delivery as stated in the histories.

In some instances more than one indication were given, but usually by reading the preliminary note it was possible to estimate their relative importance, and the classification has been made according to what seemed to be the most important in the individual case.

TABLE 8.—INDICATIONS FOR OPERATIONS.

Group A—Possibly due to the position.		
	Number.	Percentage.
Delay on the perineum.....	34	23.29
Delay in mid-pelvis.....	31	21.23
Maternal exhaustion.....	23	15.75
Group B—Not due to the position.		
Pelvic dystocia.....	17	11.64
Eclampsia and toxemia.....	13	8.90
Placenta prævia and premature separation of the placenta.....	6	4.11
Cardiac disease.....	5	3.42
Fetal asphyxia.....	6	4.11
Prolapsed cord.....	4	2.74
Twin pregnancy.....	2	1.37
Ventro-fixation of uterus.....	1	0.68
Various rare conditions.....	4	2.74
	146	99.98

Of these, only the cases in Group A can possibly be considered as being due, even in part, to the position itself. Moreover, in the 88 operative cases in this group, there were 18 forceps deliveries performed after spontaneous rotation to the symphysis or to the obliquely anterior position had occurred. This fact of the spontaneous conversion into the favorable anterior variety removes these cases from the category of those in which the original posterior position was a factor in determining the need for intervention. This reduction leaves 70 cases in which the need for operation could possibly be attributed to the posterior position. This represents 47.94 per cent of the 146 operative cases, or 11.02 per cent of the entire series, but it must be remembered that other factors, such as inertia uteri and rigid perineum, were undoubtedly responsible for a certain rather large share. Any attempt to divide the cases of delay in mid-pelvis and on the perineum, on the basis of inertia or rigidity, introduces such a large personal element, unless all observations are made by the same individual, that no such classification was attempted. Even disregarding the possible reduction in this direction, it is very apparent that occiput posteriors should rarely of themselves offer definite indications for operative procedures.

If our series of cases is divided into two parts approximately at the middle, we find that the operative frequency in the second half is appreciably smaller than during the years preceding, and that the three indications for operations in Group A, possibly indicative of dystocia due to the position, are less in evidence. Thus, in the first part—326 cases—the operative frequency was 25.1 per cent (82 operations), and 55, or 67.0 per cent, of the operations were done for Group A indications. In 12 of these cases there had been a spontaneous anterior rotation, which reduced the percentage to 52.4 per cent. In the second part—309 cases—there were 64 operations, 20.7 per cent, and 33, or 51.6 per cent, were done for Group A indi-

cations. In 6 cases there had been spontaneous rotation anteriorly and the corrected percentage is only 42.2 per cent.

This interesting reduction in operative frequency is indicative of the greater conservatism which has come with a fuller appreciation of the resources of Nature in dealing with cases with the occiput obliquely posterior. At the present time, all vertex presentations are viewed as equally benign, and absolutely no apprehension is felt when an occiput posterior is diagnosed. As is seen, the great majority of the uncomplicated cases terminate in spontaneous delivery. With the exception of low forceps, which is viewed as an almost uniformly successful operative procedure, operations are usually deferred until there is a maternal or fetal indication and, unless the duration of labor is very markedly prolonged, operations are not done on a pure time indication.

Infant Mortality.—The gross infant mortality, including all children in the series which were still-born or died during the first two weeks, was 52, or 8.17 per cent. The causes of death, as accurately as could be determined, are shown in the following table:

TABLE 9.—CAUSES OF INFANT DEATHS.

	Number.	Percentage.
Prematurity	12	23.1
Operation (no other cause evident)	11	21.1
Syphilis (macrated fetuses)	9	17.3
Still-born (spontaneous labor)	5	9.6
Eclampsia	3	5.7
Prolapse of cord	3	5.7
Placenta previa	3	5.7
Congenital anomalies	3	5.7
Died after birth (cause unknown)	2	3.9
Premature separation of placenta	1	1.9
	52	99.7

Of this total of 52, 24 weighed less than 2500 gm., and consequently may be excluded, leaving 28 deaths in the 564 mature children—a percentage of 4.96. When this is compared with Williams' figures for the total infant mortality in the first 10,000 cases in the Obstetrical Service of the Johns Hopkins Hospital, it is seen to be not much greater. He found 3.71 per cent of deaths among the mature children, using 2500 gm. as the lower weight limit for maturity. A comparison of these figures would indicate that the infant mortality is increased about 1.0 per cent in the cases of occiput posterior.

An analysis of the 28 deaths among the mature infants shows:

TABLE 10.—CAUSES OF DEATH IN MATURE CHILDREN.

Operation (no other cause evident)	11
Still-born (spontaneous delivery)	5
Eclampsia	3
Placenta previa	3
Prolapse of cord	2
Syphilis	2
Died after birth (cause unknown)	1
Congenital anomaly	1

In this series, only those deaths incident to operation, 11 in number, and those due to asphyxia in which labor was spontaneous, 5 in number, can be regarded as in any way dependent upon the position. Thus, 2.83 per cent of the mature children

perished as a result of delivery. Considering that five of these cases were complicated by contracted pelvis, it is seen that the child presenting with the occiput obliquely posterior has a chance of survival that is but little smaller than if the laws of gravitation or accommodation had ordained an anterior variety.

Duration of Labor.—The total duration of labor and the duration of the second stage were noted, whenever given, and the averages in the various classes of cases appear in the following tables. In the first place the usual arithmetic averages were computed and then an attempt was made to establish the various modes. Statisticians prefer the latter method as indicating much more closely the probabilities in any particular case. The arithmetic average is computed by adding the durations of the labors in the series and then dividing by the number of cases, whereas the mode is established by separating the cases into groups according to the duration of labor and determining in which group the greatest number of cases appear. If there is a sufficient number of cases the curve, if one be plotted, will rise gradually to the mode and then fall away on the other side.

TABLE 11.—ARITHMETIC AVERAGES FOR DURATION OF LABOR AND SECOND STAGE.

Para.	Rotation.	Labor.	No. of Cases.	Duration of Labor.	No. of Cases.	Duration of 2d Stage.
Primiparæ	Anterior	Spontaneous	186	18 hr. 27 m.	186	1 hr. 29 m.
Primiparæ	Anterior	Operative	55	29 hr. 11 m.	52	3 hr. 1 m.
Primiparæ	Posterior	Spontaneous	39	17 hr. 13 m.	39	1 hr. 30 m.
Primiparæ	Posterior	Operative	8	15 hr. 39 m.	8	3 hr. 17 m.
Multiparæ	Anterior	Spontaneous	221	12 hr. 00 m.	220	50 m.
Multiparæ	Anterior	Operative	16	21 hr. 25 m.	17	2 hr. 52 m.
Multiparæ	Posterior	Spontaneous	29	11 hr. 54 m.	28	1 hr. 4 m.
Multiparæ	Posterior	Operative	9	12 hr. 32 m.	9	2 hr. 33 m.

It is noted that in all classes the arithmetic average of the duration of labor is somewhat longer than the figures usually given for normal labor, but still the difference is very moderate. It is interesting that, in those cases in which spontaneous labor followed rotation of the occiput into the hollow of the sacrum, the duration of labor was shorter than in the cases of anterior rotation with spontaneous delivery. In the primiparæ, the duration of the second stage was almost identical whether the occiput rotated anteriorly or posteriorly, and in the multiparæ posterior rotation only slightly prolonged this stage. It was thought that backward rotation would considerably delay delivery, but these figures would indicate that there is no basis for the frequent statement that this anomaly of mechanism seriously prolongs labor.

The arithmetic average of the duration of the second stage in the various groups of operative cases is more than twice as great as the duration of this stage in the spontaneous cases. Each case is given a definite test of labor before operation is considered, and this test consists of a reasonably long second stage. Realizing that a moderate prolongation of the stage of expulsion often makes possible a spontaneous delivery, the patient is given every reasonable chance to deliver herself. In the presence of a maternal or fetal indication, prompt delivery is effected, but in the normally progressing case a very conservative course has been followed, and with gratifying results.

A further analysis was made to determine, in cases of spontaneous delivery, what percentage of labors were protracted beyond the average and what the duration of the longest and shortest labors was in the various groups. The average figures given in Table 11 were employed as a basis for comparison.

TABLE 12.—SHOWING THE NUMBER OF LABORS ABOVE AND BELOW THE AVERAGE DURATION, TOGETHER WITH THE DURATION OF THE SHORTEST AND LONGEST LABORS IN EACH CLASS OF SPONTANEOUS DELIVERY.

Primiparæ, anterior rotation.						Multiparæ, anterior rotation.					
Labor.			2nd Stage.			Labor.			2nd Stage.		
No.	%		No.	%		No.	%		No.	%	
Above average...	73	39.25	74	39.79	85	38.64	82	37.10			
Below average...	113	60.75	112	60.21	136	61.54	136	62.90			
Shortest duration 2 hrs. 10 m.											
Longest duration. 85 hrs. 0 m.											
			10 m.			45 m.			5 m.		
			22 hrs. 0 m.*			90 hrs. 0 m.			4 hrs. 20 m.		

* A neglected case brought into the Hospital as a last resort.

Primiparæ, posterior rotation.						Multiparæ, posterior rotation.					
Labor.			2nd Stage.			Labor.			2nd Stage.		
No.	%		No.	%		No.	%		No.	%	
Above average...	12	40.0	11	36.66	10	34.49	9	31.03			
Below average...	18	60.00	19	63.34	19	65.51	20	68.97			
Shortest duration 4 hrs. 10 m.											
Longest duration. 72 hrs. 0 m.											
			15 m.			2 hrs. 15 m.			15 m.		
			5 hrs. 0 m.			39 hrs. 0 m.			2 hrs. 45 m.		

Approximately two-thirds of all the cases fall below the average in the various groups, indicating no general prolongation of labor or of the second stage. Moreover, the fact that only about 40 per cent of the cases rise above the arithmetic average would indicate that a true average would fall somewhat below that figure. Because of this fact an effort was made to establish a mode in the various groups of spontaneous labors, but on account of the comparatively small number of cases this was not entirely satisfactory. Table 13 indicates the results obtained by dividing the various types of labors into groups, each group representing three hours of time.

TABLE 13.—THE MODE IN THE DURATION OF SPONTANEOUS LABORS.

	Under 6 hrs.	6-9 hrs.	9-12 hrs.	12-15 hrs.	15-18 hrs.
Primiparæ, anterior rotation....	14	24	25	30	19
Primiparæ, posterior rotation....	3	5	6	1	3
Multiparæ, anterior rotation....	61	48	27	25	20
Multiparæ, posterior rotation....	8	9	4	2	0
	18-21 hrs.	21-24 hrs.	24-27 hrs.	27-30 hrs.	More than 30 hrs.
Primiparæ, anterior rotation....	19	11	11	14	19
Primiparæ, posterior rotation....	4	1	2	0	3
Multiparæ, anterior rotation....	14	5	10	5	7
Multiparæ, posterior rotation....	1	0	3	1	1

Table 13 well illustrates the difference between the arithmetic average and the mode, and shows how the latter indicates the probabilities in a given case much more accurately than the former. For example, the arithmetic average in primiparæ with anterior rotation and spontaneous delivery (Table 11) is 18 hours 27 minutes, and yet from Table 13 it is evident that there is a greater probability of such a labor ending after 12 to 15 hours than during any other 3-hour period, and that this period consequently more nearly constitutes an average than does any other. Likewise, in the cases of multiparæ with anterior rotation and spontaneous delivery the arithmetic average is 12 hours, whereas, disregarding the period up to 6 hours (Table 13), it is seen that more labors end in the 6- to 9-hour period, and consequently this is more nearly the correct average. In the smaller groups of cases with spontaneous labor following posterior rotation, the mode is not very clearly defined, but there is evident the same tendency for it to fall below the arithmetic average.

Table 14 illustrates the results of an attempt to find the mode in the duration of the second stage in the various types of cases. Fifteen-minute intervals have been arbitrarily chosen.

TABLE 14.—THE MODE IN THE DURATION OF THE SECOND STAGE.

	15 m. or less.	16 m. to 30 m.	31 m. to 45 m.	46 m. to 1 hr.	1 hr. 1 m. to 1 hr. 15 m.
Primiparæ, anterior rotation.....	9	13	31	35	16
Primiparæ, posterior rotation.....	1	5	5	5	1
Multiparæ, anterior rotation.....	49	59	29	31	13
Multiparæ, posterior rotation.....	5	4	6	5	..
	1 hr. 16 m. to 1 hr. 30 m.	1 hr. 31 m. to 1 hr. 45 m.	1 hr. 46 m. to 2 hr.	2 hr. 1 m. to 2 hr. 15 m.	over 2 hr. 15 m.
Primiparæ, anterior rotation....	22	14	19	8	19
Primiparæ, posterior rotation....	2	2	4	1	4
Multiparæ, anterior rotation.....	13	9	5	3	10
Multiparæ, posterior rotation....	2	1	1	1	4

Here again the value of the mode as evidencing possibilities is brought out. In the primiparæ with spontaneous delivery following anterior rotation, the arithmetic average for the duration of the second stage is 1 hour 29 minutes, whereas the mode (Table 14) falls in the period between 46 minutes and 1 hour. Also, in the multiparæ with anterior rotation and spontaneous delivery, the mode falls between 16 and 30 minutes, whereas the arithmetic average is 50 minutes. In the other two classes the number of cases is too small for the satisfactory determination of the mode, but the general tendency for it to be below the arithmetic average is to be noted.

Type of Pelvis.—In an attempt to determine whether any particular type of pelvis is more apt to produce the occiput-posterior positions, the incidence of the various varieties of

pelvic deformity in the present series was determined and compared with the figures recently published by Thoms for a series of 4000 unselected consecutive cases from the Johns Hopkins Hospital:

TABLE 15.—INCIDENCE OF VARIOUS TYPES OF CONTRACTED PELVIS.

	In Present Series, 645 Cases.		In Thoms' Series, 4000 Cases.	
	No.	Per Cent.	No.	Per Cent.
Generally contracted	66	10.39	391	9.77
Simple flat	14	2.20	59	1.47
Typical funnel	36	5.67	211	5.27
Generally contracted funnel.....	15	2.36	87	2.17
Rachitic	26	4.09	186	4.65
	157	24.71	934	23.33

It is seen that the frequency of the various types of contracted pelves in the cases with occiput posterior is within 1.0 per cent of the frequency observed in the larger series of unselected cases. This indicates that the character of the pelvis has no influence upon the production of these positions.

Size of the Children.—All the cases of definite occiput posterior were used for the study, irrespective of the size of the child. For the sake of completeness, the following table is introduced to show the weights of the children in the series:

TABLE 16.—WEIGHTS OF THE CHILDREN IN THE SERIES.

1000 g. or under.....	4
1001 to 1500 g.....	8
1501 to 2000 g.....	13
2001 to 2500 g.....	46
2501 to 4000 g.....	504
4001 g. and over.....	54
Weight not recorded.....	6
	635

The only bearing that the size of the child seems to have is that, as has already been mentioned, in the case of small children the occiput tends to rotate into the hollow of the sacrum.

Maternal Morbidity and Mortality.—Our morbidity statistics are based upon a standard of 38° C. (100.4° F.), the temperature being taken by the mouth every four hours, day and night, for nine days, and then twice daily (8.00 a. m. and 8.00 p. m.) for the next five days. Special conditions may make advisable the taking of the temperature more frequently, but it is never taken less frequently. Only a single elevation above the standard is needed to have the case classed as febrile. No elevations after the 14th day are included, as they very rarely can be attributed to the labor. The following table shows the findings as regards morbidity:

TABLE 17.—MORBIDITY.

Total cases with temperature 100.4° F. or above at any time	233	36.7%
Single initial rises (normal 24 hrs. after delivery) ..	37	5.8%
Other single rises (elevated less than 24 hrs.).....	66	10.4%
Probable uterine infections.....	105	16.5%
Various other causes (eclampsia, pneumonia, mastitis, etc.)	25	4.0%

The term "single initial rise" refers to that temporary rise of temperature which so frequently occurs after a normal labor and which disappears within 24 hours, not to recur. The single rises occurring later in the puerperium and persisting for less than 24 hours can not be classified etiologically. Usually there are no symptoms and no objective findings, and within 24 hours or less the elevation has disappeared. It seems permissible to say that they are not due to a local infection of the generative tract. The 105 cases, grouped as "probable uterine infections," include all the cases which showed more than a single rise and in which a definite cause for the elevation could not be located elsewhere. That they were essentially very mild in character is indicated by the fact that there were no deaths attributable to infection. Many cases were put in this class, even when a uterine culture had failed to give any evidence of an infection, but since they could not clinically be placed elsewhere, they are included here, on the theory that a temperature elevation during the puerperium means infection of the generative tract, unless some other cause can be found.

There were in all 10 deaths in the series, a percentage of 1.57, but none of them can be attributed to the position, as the list below will show. It was not to be expected that there would not be any mortality connected with these cases.

TABLE 18.—CAUSES OF MATERNAL DEATHS.

No. 1177. Died two hours after spontaneous delivery. Chronic nephritis with convulsions.

No. 1297. Died a few hours after delivery from internal hemorrhage due to incomplete rupture of the uterus caused by manual dilatation of the cervix in the presence of a complete placenta prævia.

No. 2229. Died on the second day from toxemia and myocarditis. Confirmed by autopsy.

No. 3287. Died on the second day from acute lobar pneumonia. Confirmed by autopsy.

No. 3928. Died three days after delivery. Eclampsia. Confirmed by autopsy.

No. 5043. Died a few hours after delivery. Eclampsia.

No. 5237. Died less than 24 hours after admission. Eclampsia.

No. 5736. Died two hours after delivery. Diabetic coma.

No. 5863. Died two hours after delivery. Eclampsia. Confirmed by autopsy.

No. 5911. Died five days after Cæsarean section for partial placenta prævia and grave chronic nephritis in a 40-year-old primipara. The autopsy showed chronic diffuse nephritis.

HISTORY AND DISCUSSION.

Introduction.—It is only within the last century that the ancient fanciful descriptions of the position of the fetus *in utero* and during birth have been generally discarded. Until 1742, when Sir Fielding Ould stated that the occiput was usually turned toward one side of the pelvis during the early stages of labor, it was taught that the fetus descended through the pelvis in the position in which it was finally born, that is, usually with the occiput directly anterior under the symphysis pubis. Ould incorrectly stated that the head was turned so that the chin rested on the shoulder, but in 1752 Smellie corrected this and asserted that the trunk and head retain their usual relations, and that there is no twisting of the neck. In

1771 Saxtorph and Solayres, independently, advanced the view that the head usually enters the pelvis in the right oblique diameter.

Baudelocque, the famous pupil of Solayres de Renhae, recognized six varieties of vertex presentations, the usual four oblique and two antero-posterior. Up to that time, engagement with the occiput directly anterior was generally thought to be the most common; but Baudelocque insisted that it was very rare. He said: "It has appeared to me that the proportion of the first (L. O. A.) to the second (R. O. A.) is as 7 or 8 to 1, and to the fourth (R. O. P.) and fifth (L. O. P.) as 80 or even 100 to 1; as to the third (O. A.) and the sixth (O. P.), they are excessively rare; although most accoucheurs have thought, and still think, that the third (O. A.) is the most natural and usual."

Naegele was the first to insist upon the frequency of occiput posterior positions and their eventual rotation to the symphysis pubis. His predecessors had recognized these positions, but had thought that they were not only very rare, but that the usual outcome was rotation to the hollow of the sacrum. He showed the incorrectness of these views and attempted the first objective description of the mechanism of labor. Most of the results of his careful work have stood the test of time, but his views on the mechanism of internal rotation have from time to time been assailed. Naegele's work really marks the beginning of our modern conceptions of the mechanism of labor.

Frequency.—The figures adduced by various authors with regard to the frequency of occipito-posterior positions vary so much that it is impossible to arrive at any very definite conclusions from the literature. The older authors, as might be expected, had very divergent views concerning the relative frequency of the various varieties of vertex presentations. Thus Naegele found 29 per cent of his vertex cases in R. O. P.; whereas Madame La Chapelle found only .0777 per cent and Madame Boivin .05 per cent. Simpson noted 22.7 per cent, and Swayne 1.04 per cent. The figures for the incidence of L. O. P. also varied markedly; thus, Naegele noted only .03 per cent, while Simpson had .60 per cent, and Swayne reported 2.79 per cent.

More recent writers have reported somewhat more comparable figures, but the percentages still vary considerably. Thus, Darbyshire found 16.0 per cent occiput posteriors in 276 vertex cases; Geddes had an incidence of 10.5 per cent in multiparæ and 20.8 in primiparæ. Botkowskaia reported an incidence of 18.5 per cent, and Ingraham one of 12.03 per cent. The last author states that Pinard observed 49.8 per cent and P. Dubois 26.33 per cent. Dimitroff, in 1056 vertex presentations, noted 29.54 per cent, 26.23 per cent in R. O. P., and 3.31 per cent in L. O. P., and quoted the following figures:

	R. O. P.	L. O. P.
P. Dubois	25.60%	0.63%
Pinard and Battaillard	26.70%	10.47%
Herrgott and Vallois	33.50%	0.45%
Corbière	26.22%	7.95%
Sentex	2.03%	0.95%

Several authors (Darbyshire, Geddes and Massini) state that occiput posterior is more common in primiparæ than in multiparæ.

The actual frequency of the obliquely posterior position of the occiput is especially hard to determine because of two factors. In the first place, there is a difference of opinion with regard to the status of the transverse positions of the occiput, and in the second place, with regard to the occurrence of R. O. A. as an original position.

Most authors do not recognize the transverse position of the occiput as an original engagement, but rather as a transitional stage in the anterior rotation of the occiput which was originally directed obliquely posterior. While it is generally admitted that, in certain forms of contracted pelvis, especially the flat varieties, engagement usually occurs with the sagittal suture directed transversely, the tendency is to consider this impossible, or at least unusual, when the pelvis is normal.

There are several objections to this view, but until transverse engagement is a generally admitted fact, it will be wise to disregard the possibility of its occurrence in any but contracted pelves. The first objection is the undoubted occurrence of transverse positions in normal pelves, while the head is still too high to have been affected by the factors that are usually advanced to explain internal rotation. Various abdominal and high pelvic structures have been brought forward as factors in the mechanism of rotation, but they have generally been discarded, and rotation is usually considered as occurring low in the pelvis. If it is admitted that the sagittal suture is sometimes transverse while the head is at the brim, we must either believe in high rotation or original transverse engagement, and the latter idea seems the more tenable.

A second objection was discovered in our statistics. Our figures show that the transverse positions are more frequent than the posteriors and the L. O. T.'s are more common than the R. O. T.'s. R. O. P. is generally believed to be much more common than L. O. P., and yet the relative frequency of the supposed transitional transverse positions is reversed and a combination of the posterior varieties with the transverse gives the same total for both the right and left positions.

Among the statistics reviewed, those of Voorhees alone contain any reference to transverse positions of the occiput, and he found very much the same figures as those reported here.

If we had added the transverse positions (21.75 per cent) to the posteriors (11.57 per cent), we could have reported an incidence of 33.32 per cent, which would more nearly agree with the figures reported by the majority of writers and with the general teaching; but in the presence of the two objections raised above, it was determined to disregard the transverse positions in this study and to consider only those in which actual posterior positions were first seen.

With regard to the status of the R. O. A. positions, very much the same difficulty appears. Naegele and those who followed him have stated that R. O. A. is an exceedingly rare primary position, and that the vast majority of the cases in which this position is diagnosed are seen late in labor after there has been partial rotation from an original R. O. P. We noted this position in 19.06 per cent of our vertex presentations, and here again find it difficult to consider them all as

representing merely a stage in the mechanism of internal rotation. The chief objection to the view that they are transitional in character is their undoubted presence high in the pelvis early in labor and the inability to explain this except by some abdominal factor which can produce partial rotation but never complete turning.

If the R. O. A.'s are added to the posteriors, we have a percentage of 30.63; but in the absence of direct evidence to show that the former are not primary, they were not considered in this study. It is quite obvious that, if both the transverse and the right anterior positions were added to the posteriors, the incidence of the latter would be 52.38 per cent, or more than half of the vertex positions. It is certainly not a fact that the occipito-posterior positions are as common as this, and yet very good authority could be brought forward to show why both of these additions should be made.

If, in our series, all the right positions are added together, we have 35.91 per cent, and the left positions total 63.77 per cent. Thus:

Right.		Left.	
R. O. A.	19.06	L. O. A.	47.61
R. O. T.	8.89	L. O. T.	12.86
R. O. P.	7.96	L. O. P.	3.30
Total	35.91	Total	63.77

These figures agree closely with the usual statement that left positions occur in 70 per cent of all vertex cases and right positions in 30 per cent. The proper division into varieties is in a confused state, however, and more study is needed to settle some doubtful points concerning the mechanism of labor and the possibilities of engagement and rotation of the fetal head.

Many of the variations in the percentages reported for the posterior positions undoubtedly are to be explained by the fact that the various authors have assumed that either the transverse or the right anterior positions represent transitional stages in the mechanism of originally obliquely posterior positions, or, on the other hand, as has been done in this study, have disregarded all the cases that did not have an actual posterior position when first seen.

Internal Rotation.—The frequency with which rotation into the hollow of the sacrum has been noted is of considerable importance; and the following figures have been gathered from the literature:

Percentage.		Percentage.	
Naegele	3.12	Halsey	2.00
Edgar	4.00	Harrar	14.00 (computed)
Massini	4.00	Dupre	4.00
Tweedy	4.10	Dimitroff	1.28
Mosher	2.00-7.00	Bataillard	1.61
Ingraham	7.00	Corbière	2.71

That we found such a high percentage of cases in which the occiput rotated posteriorly may be explained by the fact that in our service operative interference is postponed as long as possible, and therefore every chance is given for spontaneous rotation in one direction or the other. Our figures (14.2 per cent) would indicate that this anomaly is somewhat more common than it is usually considered to be.

In some studies, persistent occiput posteriors (obliquely and in the hollow of the sacrum) have been noted, and it is interesting to see how the results vary. Harrar says that 20 per cent remain posterior. Stark gives 50 per cent, whereas Voorhees found 104 such cases in 5000 deliveries, approximately 10 per cent, if vertex presentations are reckoned at 95 per cent and occiput posteriors as 20 per cent of these. Bill says that 50 per cent fail to rotate, and Rice noted 162 failures in 400 cases of occiput posterior, or 40.5 per cent.

By reference to Table 3, it is evident that there were 157 cases out of 576 in which the occiput failed to rotate, *i. e.*, stayed transverse or obliquely posterior, or rotated into the hollow of the sacrum. This would give us a percentage of 27.25 of so-called persistent occiput posteriors. This is a very considerable number, but it must be remembered that in nearly half of these cases the occiput rotated into the hollow of the sacrum, and this was followed in a large majority (88.6 per cent) of the cases by spontaneous delivery. If the term "persistent occiput posterior" be used only in referring to those cases in which the occiput rotates neither to the symphysis nor to the sacrum, we can very readily realize their importance, for internal rotation is one of the cardinal movements in the mechanism of labor and under ordinary conditions delivery can very rarely occur without it.

The Mechanism of Internal Rotation.—It was found, as previously stated, that the parity of the patient and the condition of the pelvic floor have no influence upon the occurrence of posterior rotation, but that the three factors which apparently do play a part are the type of the bony pelvic outlet, the flexion of the head, and its size.

An attempt was made to correlate these observations with some one of the theories of internal rotation that have been advanced. From the fact that anterior rotation is as common in multiparæ as in primiparæ, it may be argued that the muscular and fascial pelvic floor plays a minimal part in the mechanism. It is conceivable that these soft pelvic structures may act to accelerate or complete a rotation already begun, but it is impossible to make this theory of Veit explain all the vagaries of rotation under the conditions which we have observed. It is very difficult to conceive a mechanism whereby the pelvic floor alone can cause anterior rotation from an occiput obliquely posterior position. On the other hand, although the failure of this usual occurrence can be explained when the head is poorly flexed or small, these explanations do not cover those cases in which a narrow pubic arch is apparently responsible for the lack of anterior rotation.

Sellheim's otherwise attractive theory falls short when he attempts to explain posterior rotation. He assumes a spastic condition of the child's neck, which makes it more readily bent backward than forward, so that, as a consequence, the occiput turns into the hollow of the sacrum. It is difficult to substantiate this by clinical observation, and the unprejudiced obstetrician cannot detect any difference in tone in the neck musculature of children born by this anomalous mechanism. Moreover, this theory offers no explanation for the more frequent occurrence of posterior rotation in those conditions which, as we have shown, conduce to its appearance.

The various abdominal and high pelvic theories offer no assistance. In view of the fact that they have been so generally discarded, they need not be discussed here in detail.

Although none of the theories will explain absolutely all cases, Hodge's idea of the inclined planes and ischial spines will at least explain anterior rotation from an obliquely posterior position and also the phenomenon of posterior rotation in the three conditions which, according to our experience, most conduce to this anomaly. Hodge says: "Hence, when the head descends in the fourth position (R. O. P.), if the point of the occiput should strike upon the spinous process of the ischium or extreme boundary of the anterior inclined plane, it will be reflected anteriorly toward the arch of the pubis, and delivery will be effected as in an original second position (R. O. A.). If, however, the point of the occiput should strike posteriorly to the spines of the ischium, it will be reflected backward to the hollow of the sacrum." In this connection it is interesting to note that Baudelocque and Deventer observed that posterior rotation was more frequent when the ischial spines protruded.

Let us now attempt to determine why it is that the three conditions mentioned have such a tendency to cause posterior rotation. In the first place, when the head descends through the pelvis poorly flexed with the occiput obliquely posterior, it is evident that the occiput is somewhat nearer the sacrum than usual and the brow is well up against the symphysis. The ischial spines will impinge upon the head considerably in front of the occiput, and the brow will be influenced by the anterior planes, while the occiput is affected by the posterior planes. Under these conditions it is easy to understand why the occiput should go backward.

When the fetal head is smaller than usual or the pelvic cavity much more roomy than normal, there is a tendency for the head to advance through the most capacious part of the pelvis, where the resistance is least. This would tend to bring the occiput behind the spines and thus to cause posterior rotation. Or, the head being very small, it is conceivable that it would not impinge upon the spines at all and consequently, by a process of accommodation to the opening in the pelvic diaphragm, it would eventually rotate backward.

Finally, when there is a narrow pubic arch, the proximity of the tubera ischii prevents the head from getting well up under the symphysis and it must find a passage more than normally behind the protruding spines. This will mean that the head will strike the spines in such a manner that the occiput will meet the posterior inclined planes and will rotate to the hollow of the sacrum.

Where the pubic arch is wider than the arbitrarily chosen upper limit for funnel pelvis (8 cm.), the ischial spines may still protrude somewhat more than usual and give a pelvis which, as regards the mechanism of rotation, should still be classed as funnel. This probably explains some of the cases of posterior rotation in normal pelvis.

Anterior rotation can occur in a funnel pelvis if the anterior planes are sufficiently long to cause the occiput in its descent to strike upon them and be deflected anteriorly. In these

cases the capacity of the posterior portion of the lower pelvic cavity is restricted, and the head is often molded considerably in order to accommodate itself between the approximated tubera.

If the posterior planes and the spines, rather than the soft pelvic tissues, are responsible for posterior rotation, this phenomenon should never occur after the head is visible. This is in accord with our observations. On the other hand, anterior rotation frequently happens after the head is crowned by the partially separated labia. The anterior planes and the spines are near enough to the vaginal orifice so that, when the vertex is visible, the widest portion of the head—the biparietal diameter—is in the region of these planes and their effect is then made evident. The position of the head at the time of internal rotation should, therefore, and does, vary not only with the length of the pubic bones, but also with the width of the pubic arch. The wider the arch, the lower the head must be before the spines and planes become effective, and the greater the possibility of visible rotation.

It is not claimed that Hodge's theory and its application in the previous paragraphs explain all the vagaries of rotation in the cases of occiput posterior, but it certainly seems to be the most attractive. In the elaboration of the theory to explain the observed facts, certain assumptions and conjectures have been indulged in which may not prove wholly acceptable. As a matter of fact, it is more than probable that no one theory will satisfy all the demands made upon it, and that the final word in the mechanism of internal rotation will embrace a skillful combination of several factors.

Rupture of the Membranes.—Although practically all writers assert that premature rupture of the membranes is more common in the posterior than in the anterior varieties of occiput presentations, very few actual statistics were found. Harrar found premature rupture 1776 times in 5496 occiput anterior cases, or 32 per cent, and in 348 out of 804 occiput posterior cases, or 43 per cent. Rice noted first stage rupture in 40 per cent of occiput anterior and in 60 per cent of occiput posterior cases. Massiri insists that premature rupture is more common among primiparæ with occipito-posterior positions than among multiparæ with the same positions. Some authors even say that premature rupture should immediately suggest occiput posterior because of the fact that it is so frequent in that position. Attempts to explain this relation have been mostly on the basis of a poor accommodation between the head and the pelvic inlet. Our figures—21.8 per cent of rupture before half dilatation of the cervix—fail to substantiate the usual opinion, and furthermore we cannot see why, theoretically, there should be any difference in the behavior of the fetal envelopes whether the occiput is anterior or posterior. If the head is well flexed when it enters the pelvis, as it undoubtedly is in the majority of cases, the same diameter engages at the superior strait and, that being the case, the fit must be the same whether the back of the child happens to be anterior or posterior.

Character of Delivery.—Treatment.—Many articles have been written upon the correct course of treatment in occiput

posterior cases, and many methods have been devised for overcoming the difficulties which have been so greatly emphasized. The very diversity of these procedures is indicative of the confusion which exists in the whole subject. Several of the methods advocated are based on sound principles, but the majority have tended only to confuse a subject which is really comparatively simple.

C. D. Meigs, in speaking of these cases, said: "Beware of meddlesome midwifery and, if one is to err in these cases, better err on the side of waiting." This bit of advice is just as true now as when it was written, but the improvements in aseptic technique, by eliminating many of the former horribly fatal results, have led to haste in obstetrical work. The knowledge of when to interfere is as important as the mere technique of performing the usual forceps operations, but good judgment is much rarer than good operative ability. The profession generally seems to have been so impressed with the statement that occiput posterior positions will very frequently need operation that they do not wait to see whether the individual case will make that demand, but proceed to deliver instrumentally on the smallest provocation, and often on none whatever.

The more conservative writers have reported a small operative incidence. Thus, Naegele noted 11.8 per cent forceps deliveries, P. Dubois 7 per cent, Battaillard 10 per cent, Dupré 3.64 per cent, Botkowskaia 10.75 per cent in primiparæ and 2.5 per cent in multiparæ. Corin gives the incidence of spontaneous labor as 96.23 per cent, Dimitroff as 93.9 per cent, Mosher as 90 per cent, and Lacroette as 87 per cent. In these series, the figures were taken from cases which were normal in every other respect, and indicate the interference necessary in uncomplicated occiput posterior labors. In an early section we have considered 11.02 per cent of our operative deliveries as possibly due to the position.

In contrast to these figures indicating that the uncomplicated occiput posterior should *nine times out of ten* be delivered spontaneously, Bill reports that 50 per cent of his cases of occiput posterior needed forceps, and details rather incompletely 137 cases in which the double application of forceps was employed. Many of these operations were done with the head still high in the pelvis and, judging from the context, through a partially dilated cervix. Again, Lukins has recently stated: "The ideal plan of management in occiput posterior positions, provided the patient can be seen and the diagnosis made sufficiently early, is to hasten cervical dilatation by manual means and accomplish immediate version by combined internal and external manipulations."

The statements in the last paragraph illustrate what an unenviable reputation the position in question enjoys, and what radical methods are introduced in order to obviate difficulties which really do not exist. Evidence might, indeed, be introduced to show that there are physicians who seriously advocate the employment of the Cæsarean section in the absence of any other indication. In the light of our experience, it is difficult to see how such errors have arisen.

Of the many published methods of treating the complication, if there really be one, very few have any sound reason to

commend them. Postural treatment, with the patient lying on the same side as the occiput or on the other side, as is variously recommended, is certainly of little value, as is attested by the lack of unanimity of opinion with regard to which side is preferable. Correcting the obliquity of the uterus by means of pads and binders seems futile. Manual rotation of the head at the superior strait and the correction of improper flexion digitally have a sound basis, but are rarely indicated. O'Brien's method of rotating the mother around the child, by fixing the latter manually, seems not only awkward, but useless, when one considers how readily the reverse can be accomplished. The double application of forceps distinctly has a place in the treatment of the unrotated occiput, but is indicated only when rotation cannot be accomplished manually. The single application of forceps with the blades reversed or reversing has no distinct field of usefulness when there are so much simpler methods that have not the obvious disadvantages of these procedures.

The chief point in the treatment is to give Nature a chance, and not to fall into the common mistake of thinking that the position itself will cause trouble. A large portion of the cases will need no assistance, and the majority of those that do demand help will offer no great difficulty. Spontaneous rotation will usually occur, but if it does not, at least 90 per cent of the heads can be rotated manually to the transverse or obliquely anterior positions and then delivered by a single application of the forceps. Podalic version is useful in certain cases, but should be reserved for those in which the indication for delivery arises while the head is still at the brim and the choice lies between high or floating forceps and version. High forceps are being more and more discarded as operators realize the excessive fetal mortality usually consequent upon the procedure. Rarely does the posterior position of the occiput itself call for interference while the head is still at the brim, and the exercise of a little more patience will usually be rewarded by its descent and eventual anterior rotation. Cæsarean section distinctly has no place in the treatment, unless there is some other definite indication, such as contracted pelvis, and then the occiput posterior is not what demands the section.

As has already been stated, we view these cases with equanimity, and, in consequence, the patient is treated exactly as if there was any other uncomplicated vertex presentation. We do not insist that she assume any particular position, nor do we attempt to apply any abdominal pads or binders. No attempt is made to correct improper flexion or to rotate the occiput forward. The spontaneous cases are, of course, simple: if the occiput has rotated into the hollow of the sacrum, it is permitted to be born as such. There is probably, in these latter cases, a greater possibility of perineal lacerations, but these are never extensive enough to be of serious moment. In applying forceps a certain routine is followed. In the first place, the vulva and vagina are manually dilated until they admit the clenched hand; a cephalic application of forceps is then made, the posterior blade being introduced first over the posterior ear with the hand in the vagina definitely feeling

the ear; the other blade being introduced posteriorly and rotated over the face to lock with the first. The patient is allowed to come partially out of the anesthetic while short intermittent but frequent tractions are made. If the occiput is directly anterior or posterior, a pelvic (of course, also, a cephalic) application is made and the head delivered directly. If the occiput is obliquely anterior or transverse, a cephalic application is made, and during the tractions a slight rotary movement of the blades accelerates rotation. With the occiput still obliquely posterior, the hand in the vagina grasps the head securely between the four fingers and the thumb, and rotation is attempted, the occiput being turned as far anterior as possible. The position of the head is immaterial, for this procedure can be successfully carried out even when the head is tight against the perineum. During the maneuver the head may be pushed up slightly, but this is rarely a disadvantage. In rather rare cases the head will not remain in its new position and falls back to the obliquely posterior position. Here one can attempt the double application with little better chance of success, or deliberately apply as for the opposite anterior position and rotate through 45° so that the occiput becomes directly posterior. Although this procedure cannot be very warmly recommended, it has a certain field of usefulness, especially in the class of cases just mentioned and in others, particularly in patients with relaxed outlets, where haste is imperative. The Scanzonian or double application of forceps is rarely necessary. The blades are first applied for the opposite anterior position and the occiput rotated forward to a transverse or an obliquely anterior position while downward traction is employed. The blades are then removed and re-applied for the new position, and delivery is completed with the occiput under the symphysis.

Infant Mortality.—In the various statistical reports that have been published, the infant mortality in the cases of occiput posterior has received considerable attention, and the general opinion seems to be that the percentage should be little, if any, higher than for other positions of the vertex. Usually the figures given represent the deaths during labor and during the first week or two of life.

Harrar gives the total infant mortality in the occiput posterior cases, including the first few days of life, as 9 per cent, Dimitroff found 7.64 per cent, Darbyshire, 15.9 per cent, and Mosher says that the mortality is raised from the usual 4 per cent in occiput anterior positions to 10 per cent, when the occiput is posterior. Edgar gives the mortality as 10 per cent, and Ingraham as 5 per cent. Our figures, 8.17 per cent, represent about the average in the other series. Our material includes about 40 per cent of colored patients, and the infant mortality among their children is always considerably higher than among the whites.

In considering the average mortality for all cases, irrespective of position, Harrar gives 5.8 per cent and Tweedy, 7.4 per cent. The figures recently published from long series of cases from the Sloane Hospital for Women and from the Johns Hopkins Hospital indicate a total infant mortality during the last two months of pregnancy and the first two

weeks of extra-uterine life, of approximately 7 per cent. This is only about 1 per cent lower than our findings in the occiput posteriors, and a difference as small as this needs no explanation. For practical purposes, then, it can be said that the infant death-rate should not be appreciably increased when the occiput is posterior.

In our series 2.83 per cent of the mature children succumbed to delivery, there being no complications which would place the infant life in jeopardy. Only 5 of the 16 babies which make up this group were delivered spontaneously, so that less than 1 per cent represents the mortality if operative measures are not required. This emphasizes the fact that the mortality is chiefly due to the measures which are employed as treatment, and, consequently, the more conservative the methods, the lower the mortality rate.

Duration of Labor.—The statement frequently made that labor is very much prolonged in the cases of occiput posterior is not only not borne out by our findings, but the figures gathered from other statistical studies would indicate that there is, at most, only a very slight increase. Thus, we have gathered from the literature the following statements of the duration of labor when the occiput is posterior:

TABLE 21.—DURATION OF LABOR.

Author.	Primiparæ.		Multiparæ.	
	Labor.	2nd Stage.	Labor.	2nd Stage.
Corinin	14.97	2.14	7.56	.35 to .45
Sentex	16.00	16.00
Bataillard	14.22	7.50
Corbière	16.12	9.42
Dimitroff	16.11	7.41
Botkowskaia	21.30	13.30
Varnier	13.30	7.30
Rice	16.30	2.10	11.30	1.40
Massini	11.15	8.12

Harrar says that the average duration of labor in primiparæ and multiparæ is 16 hours, and of the second stage 1 hour and 35 minutes.

It would not be surprising if labor were somewhat prolonged, especially when it is considered that rotation takes place through an arc of 135° rather than through 45° ; and that when the occiput rotates posteriorly the dilatation of the outlet by a larger diameter of the head would tend to prolong labor. Williams gives the average duration of labor in primiparæ as 18 hours and of the second stage as 1 hour and 45 minutes, and his figures for multiparæ are 12 hours and 1 hour respectively. Our figures (Table 11) correspond so closely with these that it cannot be said that there is any definite prolongation due to the position.

Although it would seem that the adaptation of the principle of the mode to statistics of this kind would serve a distinct purpose in indicating more accurately the probabilities with regard to the duration of labor in any given case, yet it apparently has not been applied and there are no figures available for comparison.

Type of Pelvis.—The type of pelvis has rarely been noted in the other statistical studies, except that some of the series

have been taken from cases with normal pelvis alone. Harrar found a "small pelvis" in 3 per cent of his cases of occiput posterior, and states that the outlet was "moderately contracted" in 72 per cent and "small" in 1 per cent. Ingraham found a slightly increased frequency of occiput posterior positions in women with contracted pelvis. Paramore states that the "small round pelvis" causes persistent occiput posteriors, and quotes Edgar as saying the same thing for a kyphotic pelvis observed by him. In the latter case, the funnel shape of the pelvis can be adduced as the cause of the lack of rotation rather than the inlet contraction, if one existed. There are no available statistics which would indicate that any one type of pelvis is especially a factor in the production of occiput posteriors. Our figures show no relation between the incidence of any type of pelvis and posterior-occiput positions. It is probable that the position of the occiput is determined solely by other factors.

Maternal Morbidity and Mortality.—A comparison of morbidity rates is always unsatisfactory because of the variations in the routine for temperature taking. It is obviously unfair to compare twice daily temperature observations with those taken every four hours, and, likewise, axillary or rectal temperatures with those taken by mouth. For that reason only the observations on other groups of cases from the same clinic are comparable, in that all the conditions are the same. The author has recently reported in an entirely different connection a series of 400 consecutive cases in which the morbidity rate was 37.8 per cent. While it might seem that the rate in the present series, 36.7 per cent, is high, nevertheless it is almost identical with the other series, thus indicating no increased morbidity in occiput posteriors, which is really the point in question. The apparently high morbidity rate can be explained by the high criterion to which each case is subjected, and by the fact that all the patients are used for purposes of instruction.

As might be expected, there is no maternal mortality attributable to the position of the occiput, and the 10 deaths in the series were so definitely due to other causes that no suspicion can be directed against the occiput posteriors.

CONCLUSIONS.

1. The frequency of occiput obliquely and directly posterior positions was 11.54 per cent in the series, although the actual percentage of cases originally in this position was probably considerably higher.

2. Rotation of the occiput into the hollow of the sacrum occurred in 14 per cent of the cases.

3. Three factors which tend to favor rotation into the hollow of the sacrum are poor flexion, small size of the head, and funnel pelvis. Contraction of the pelvic inlet favors anterior rotation.

4. The etiology of internal rotation is not satisfactory, but Hodge's theory of the ischial spines and inclined planes is the most acceptable.

5. Premature rupture of the membranes was not especially frequent when the occiput was posterior.

6. Spontaneous delivery was the usual outcome. The total operative incidence was 22.9 per cent, but in only 11.02 per cent was the position possibly accountable for the need for intervention.

7. There was no increased infant mortality because of the posterior position.

8. Labor was not prolonged, independently of whether the occiput rotated to the symphysis or into the hollow of the sacrum.

9. A contracted pelvis did not increase the incidence of the posterior positions.

10. There was no additional maternal morbidity or mortality.

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A LETTER OF EDWARD JENNER CONTAINING A BRIEF ACCOUNT OF HIS DISCOVERY OF VACCINATION.*

By CHARLES M. MCBRYDE, M. D., Washington, D. C.

The communication I have to present this evening consists of a letter which was found among some old family papers. The letter was written by Edward Jenner, the discoverer of vaccination, to my great grandfather, John Bolton, who at the time was a prominent citizen of Savannah, Georgia. In the years 1802 to 1806, Mr. Bolton and his wife, who is referred to in the Jenner letter, spent some time in traveling abroad. During a visit to England in 1805, Mr. Bolton appears to have placed himself under the professional care of Dr. Jenner, who had then achieved a conspicuous place in the medical world of the day. Mr. Bolton was in London at the time he received the letter and had evidently consulted Jenner at Cheltenham at an earlier date, probably a short time previously. The first portion of the letter, that is, the letter proper, is of a purely personal nature, pointing out the probable origin of Mr. Bolton's ailment and giving rather full and explicit directions in regard to diet and exercise. The second portion of the letter, or rather the postscript, which is somewhat longer than the letter itself, and deals with the subject of Jenner's great discovery, is the part of especial interest. I shall, however, give you the whole letter, as it will doubtless be of interest to most of you to hear

Dr. Jenner's advice in regard to diet and exercise and it may also be of interest to some of you to speculate on the probable nature of the complaint for which Dr. Jenner prescribes. In this connection I will state that Mr. Bolton was 31 years of age at the time. That the ailment from which he suffered was not of a serious nature is attested by the fact that he lived for 33 years thereafter, attaining the age of 63 years, but perhaps this was due to the fact that he was careful to follow out the course of life laid down for him by the "father of vaccination." The letter, while perfectly legible, is considerably worn and hardly in condition to pass among the audience. I have therefore had lantern slides made from it and will have these thrown on the screen. I will read the letter slowly and feel sure you will have no difficulty in following it on the screen.

The letter was folded and sealed with a black wafer. It is addressed to "John Bolton, Esqr., York Hotel, New Bridge Street, Black Friars, London." It is stamped "Cheltenham 10 D" and is postmarked "Sept. 26, 1805." The letter is as follows:

Cheltenham Sept. 8th 1805

My dear Sir

After maturely considering the nature of your complaints, I am strongly induced to think that all of them arise from a debilitated state of the stomach & bowels. What then is to be done to recall

* Read before a meeting of The Johns Hopkins Hospital Historical Club, March 8, 1915.

that suspended energy which is so essential not only to life itself but to that correct movement of the vital organs in general, on which the comforts of life depend? This I shall endeavor to point out. Some medicinal treatment will certainly be necessary, but this will not be so essential as the strict observance of the rules of diet: the former indeed unaided by the latter will in my opinion be of little avail. Recollect then my injunctions when at Cheltenham. To be very sparing in the use of such food as experience tells us has a tendency to become either acid or flatulent, such as Garden Vegetables in general, Fruit, Pastry, melted butter, beer & cider etc. & in their stead to live chiefly on such food as will not only afford more nutrition but give less disturbance during digestion. Of this description is animal food. You need not be very choice in your selection—past experience will point out that which agrees best with you. Exercise is very conducive to digestion, and this you will take either on foot or Horseback in a regular way. But you must avoid those exertions which will bring on any great degree of lassitude. I know nothing so likely to correct your costive habit as the artificial Cheltenham Water prepared with the chalybeated Cheltenham Salts—& nothing so proper as opium if at any time you should feel the spasm that has so long annoy'd you, in any degree of violence. Enclos'd is a Prescription for the Chalybeate I mentioned, and from its use in conjunction with the other restorative means pointed out, I expect you will derive that amelioration in the state of your health which will afford me pleasure to hear of on a future day. This medicine will keep well in a vial—you may take forty grains of it twice a day mixt with any thick substance, such as Honey, Molasses or gruel. I have also enclos'd a Prescription for Mrs Bolton, from which I trust she will derive great advantage, and if she could bring herself to relish a diet of a kind similar to that I have recommended to you, I feel confident of its proving essentially useful to her.

Believe me dear sir, with every good wish your obliged and very faithful humble servant

Edw^d Jenner

P. S. The greater part of this letter was written when dated; but from a series of unavoidable interruptions I have been driven to the necessity of not finishing it till now. I trust it will reach you before you leave England.

You were good enough to express a wish during our conversation on the subject, to be acquainted with my History as far as relates to the vaccine discovery. I will therefore give you the following outline. Pray make what discretionary use of it you please, but don't publish it; at least don't print it, as I think it would dishonor my country.

Near thirty years ago, my researches into the nature of the Vaccine disease commenc'd. Although much accustomed from my earliest years to the investigation of subjects in Natural History, I found this so involv'd in obscurity, so intricate and complex that I did not develop it to my complete satisfaction till the year 1798, when, in a publication, entitled "An Inquiry into the causes and effects of the Variolæ Vaccinæ or Cowpox" I immediately laid the whole before the world. My situation at this time was that of a physician in full and lucrative practice in my native County, Gloucestershire. But being necessitated to quit my situation in the country and live in London in order to establish the new practice, my increas'd expenses and the separation from my former professional income reduced my possessions from a state of plenty to that state which gave me some alarm. In this situation I made an application to Parliament and was heard. £10,000 was the sum proposed by one member as a compensation and 20,000 by another. The lesser sum was voted, the minister, Mr. Addington, alleging that he should certainly have consented to a grant of the larger sum but was well convinced that my practice in town would speedily and amply remunerate me. I made the Trial and

according to my own expectations, failed. It could not well be otherwise, as I had concealed nothing, but on the contrary took the greatest pains during my residence in Town to make everyone as good a Vaccine Inoculator as myself. Whereas, had I (looking forward to the amassing of Riches more than diffusing the incalculable advantages of the Discovery) kept it a secret, my Fortune might have been made to any extent. This opinion was given in evidence before the Committee of the House of Commons by some of the first medical Gentlemen in the Metropolis.

I am now again a Resident for the most part in Gloucestershire, and from a combination of circumstances which I need not detail am doom'd to feel the pressure of an expense of more than £500 per annum without scarcely any provision being made for me, the vote of Parliament having done little more than make up the losses and expenses incur'd in the prosecution of that Inquiry which led to the fortunate discovery and establishment of Vaccine Inoculation, a discovery which I trust I may be allowed exultingly to say will add more to the stock of human happiness than any that has preceded it.

E. J.

Just a few words in closing as to why Jenner took pains to set forth these facts in regard to his discovery and why he admonished Mr. Bolton not to publish the letter. The tone of the letter shows very clearly that Jenner at this time was much dissatisfied with the grant of £10,000 awarded him by Parliament and that he regarded this sum as an inadequate reward for the time and labor he had spent in prosecuting his investigations, which, as he states in the letter, covered a period of 30 years and had placed him under heavy expense, hence his admonition not to publish the letter for fear it would reflect upon his country. This feeling of bitterness toward his country was doubtless afterward dissipated when Parliament, recognizing his just deserts, made him a second grant of £20,000 in 1807. Furthermore, at about this time his friends and admirers in other parts of the world were endeavoring to raise popular subscriptions in his behalf, in order to testify their appreciation of the value of his great discovery. Thus, in 1812, he received a subscription of £7383, which was raised in India where his discovery had been gratefully received. A similar undertaking was set on foot in France by Dr. Valentine, of Nancy, a friend and admirer of Jenner's, but this effort appears to have come to naught. It seems not improbable that Mr. Bolton may have had some plan of this sort in mind for the United States, where at this time vaccine inoculation had become well established, thanks to the efforts of Dr. Waterhouse, President Jefferson and others. The fact that Jenner prefaces the outline of his discovery with the words, "pray make what discretionary use of it you please," suggests that Mr. Bolton in the course of his conversation with Jenner at Cheltenham may have indicated that he could make use of these facts in America. This is mere supposition, however, and I do not know whether any steps were ever taken looking toward a popular subscription in this country.

As far as I know Jenner's request has been respected and this letter has never been published, but in view of the fact that he finally received an adequate reward from his government and became the recipient of innumerable honors, both at home and abroad, there is certainly now no fear that this country will suffer criticism from its publication.

Chatterham, Sept. 10, 1916

Dear Sir,

After carefully re-considering the nature of your complaint, I am strongly inclined to think that all of them proceed from a debilitated state of the stomach and bowels. What has to be done to insure that condition may be which is so important not only to the body but to that correct movement of the vital organs in general, on which the comfort of the depends. Thus I shall endeavor to point out. Some medicinal treatment will certainly be necessary, but this will not be so important as the strict observance of the rules of diet; the former indeed unwielded by the latter will in my opinion be of little avail. Recollect then my instructions when at Chatterham to be very sparing in the use of such food as experience

Chalybeate I mention, and from its use in conjunction with the other restorative means pointed out. I expect you will desire that amelioration in the state of your intellect which it will afford me pleasure to hear of on a future day. This medicine will keep well in a vial - You may take forty grams of it three a day, mixed with any thick substance, such as Honey, Molasses, or gruel. I have also enclosed a Prescription for Mrs. Bolton, from which I trust she will derive great advantage. And if she could bring herself to relish a diet of a kind similar to that I have recommended to you, I feel confident of its proving especially useful to her.

Believe me dear Sir, with every good wish your obliged & very faithful humble servant,
Edw. Jenner

tells us has a tendency to become either acid or flatulent, such as garden vegetables in general, Trinit, Potato, milled Baker, Beer &c. &c. & on this head to live chiefly on such food as will not only afford more nutriment but give less disturbance during digestion. Other description is animal food. You need not be very choosy in your selection - Past experience will point out that which agrees best with you. Exercise is very conducive to digestion and this you will take either on foot or horseback in a regular way. But you must avoid those exertions which will bring on any great degree of fatigue. I know nothing so likely to counteract our cosine habit as the Chatterham Water prepared with the Chalybeate Chatterham salts - & nothing so proper as Opium if at any time you should feel the spasm that has so long annoyed you, in any degree of violence. Enclosed is a Prescription for the

P.S.

The greater part of this letter was written when dated, but from a series of unavoidable interruptions I have been unable to finish it. I am now in the receipt of your letter of the 10th inst. & I shall reach you before you leave England.

You were good enough to express a wish during our conversation on the subject, to be acquainted with my history as far as relates to the vaccine disease. I will therefore give you the following outline. Please to send me a list of the names of the persons to whom I may send the vaccine virus, and I will send it to them as soon as possible.

As I have now a good number of vaccinees in the hospital, I have decided to send you a small number of vaccinees from my

earliest years to the investigation of 'objects in Natural History, I found this so involved in obscurity, so intricate & complex, that I did not devote it to my complete satisfaction till the year 1790, when, in a publication, entitled "An Inquiry into the causes and effects of the Varicellæ Vaccina or Cowpox" I immediately laid the whole before the world. My situation at this time was that of a Physician in full and lucrative practice in my native County of Gloucestershire. Not being satisfied to quit my situation in the country and live in London in order to establish the new practice, my increased expenses, and the ^{small} ~~rather than my former~~ ^{official} income, reduced my possessions from a state of plenty to that state which gave me some alarm. In this situation I made an application to Parliament and was heard. £10,000 was the sum proposed by one Member as a compensation and 20,000 by another. It was

The work of Pollock had having done little more than make up the losses and expenses incurred in the prosecution of that inquiry, which led to the fortunate discovery & establishment of Vaccines. I now feel it a duty to begin with add mine to the stock of human happiness than our kind that has preceded me.

29

I am was asked, the President of the Association, saying
 that he should certainly have been consulted to a
 report of the paper but was well convinced
 that my paper on this would excite and amply
 remunerate me. I made the trial and according
 to my own expectations failed. It could not well
 be otherwise as I had concealed nothing but on the
 contrary took the greatest pains during my residence
 in Iowa to make every one as good a Vassar. I would
 as myself. Whereas had I (looking forward to the
 imaging of Rhode more than to the innumera-
 ble advantages of the Discovery) kept it a
 secret, my Fortune might have been made to our
 extent. This opinion was given in evidence
 before the Committee of the House of Commons by some
 of our ~~English~~ medical brethren on the 14th of the 11th.

I am now again a Resident for the most part in Gloucestershire, and from a combination of circumstances, which I need not detail are doomed to spend the greater part of an expense of more than £50 per annum without scarcely any provision being made for me.

A REPORT OF SIXTY-FOUR CASES OF EPILEPSY IN PATIENTS FROM FOURTEEN YEARS TO FORTY YEARS OF AGE.

By L. R. WATERS.

Social Service Department, Johns Hopkins Hospital.

From January 1, to September 1, 1915, there applied to the Neurological Dispensary of The Johns Hopkins Hospital, for treatment, 173 people who were suffering from epilepsy.

Of this number, 64 between the ages of 14 and 40 were taken at random for a social study. No effort was made to select cases which seemed especially interesting. The ages from 14 to 40 were chosen because between these limits one is supposed to be of the greatest economic value to the community. In gathering the following information, each patient was interviewed in the dispensary, then the home was visited, and interviews were held with relatives and friends, and in some cases with school-teachers and employers. From this study it was hoped to show in a small way the need of an institution for those suffering from epilepsy, where the patient could be protected, trained and studied.

As shown by the summary of the statistics gathered, in a large majority of the cases, the onset of the trouble appeared before the twelfth year. Of the 64 patients, 57 had made some attempt at an education, but 30 of these had been obliged to leave school because of their epileptic attacks. As regards the grades reached before leaving school, five got no further than the first grade, and one reached the first year of college. The greatest number for any one grade was 15 in the fourth grade. Thirty-eight attended the public schools, and 19 were in the parochial schools. Investigation has shown that the parochial schools are more willing to keep epileptic children in their classes than are the public schools. For a very short period of time the public schools had two or three special classes for epileptics, but they were soon disbanded as they were not found practical. The pupils for these classes were drawn from the entire city, and either had to have someone take them to school and call for them, or else they had to go alone. Many of them had attacks on the way to and from school; there were several accidents; for the most part parents were afraid to have their children attend these classes. Consequently, a great number suffering from epilepsy received no education at all. Even though the statistics show that many of them had reached grades in which they should have been able to read and write, investigation has proven that few of them actually read and write; nor do the parents attempt to teach them anything at home. From the time of the first attack, they are treated differently from other members of the family, and no effort is made to help them to find life pleasant in any way. To use the words most often employed in describing their life—they "just sit around."

Twelve of the 64 have married, seven men and five women. Five, two men and three women, gave as a reason for marrying that they had been told that marriage would cure them of epilepsy. All seven of the men are working and supporting their wives. Three of them have regular employment, but the

other four are in constant dread of losing their work. In only one case, that of a colored man, has the wife deserted. Four of the men are fathers of healthy children. Three have no children. None of the married women work away from home. Four of the women are supported by their husbands, and one by relatives. One woman had an epileptic attack during the marriage ceremony. The ceremony was halted until her recovery and then completed. Her husband deserted her six months later, and she had to return to relatives for care. Another of the women gave birth to an illegitimate child when 15 years old, has since been divorced from one man, and is again married. She has syphilis and her mental state is poor. She is responsible for the training of her own illegitimate son of 14 years and a 10-year-old stepdaughter. Only two of the married women have given birth to children—the one mentioned above, and another who is the mother of four children, three of whom have epilepsy and the fourth lung trouble. All of the patients mentioned, both men and women, were married after epilepsy had developed.

Twenty of the 64 patients have never been able to even attempt work. Forty-four have tried everything, from errand boy to foreman in a clothing factory. In no case had there been any attempt at special training. Of the 44 who began work, only 15 persevered for any length of time. Of these 15, three have never been advanced in salary, one has been decreased, and 11 have been increased. Seventeen of the families have been registered as asking help from some local agency.

No mental test was made of any of the patients, but in only nine of the cases did the mental condition appear normal. In 17, the mental state seemed fair and in 38, poor.

In 17 of the families, there was more than one person suffering from epilepsy.

Thirty-eight of the 64 patients quite obviously need institutional care.

Almost every story heard was a tragedy. Invariably some member of the family, usually the mother, has to devote her entire time to the patient. He can never be alone, and yet there is no place for him. The schools will not have him; the public amusements do not welcome him; and he is even discouraged from going to church; so that, untrained, he necessarily must "just sit around." One mother told of her constant fears for her 16-year-old boy, a strong, good-looking lad, who could not get work but who spent his time ogling the little girls of the neighborhood. Another mother tells of having her life "wrecked" by her epileptic daughter, for whom the state makes no provision, who has already given birth to one illegitimate child, and who is entirely unmanageable.

There are many stories of families suffering privations in order that the \$3 or \$4 may be forthcoming each month to buy the patent medicine which is guaranteed to cure "fit."

A similar story is told by a mother who has spent all of her savings, several thousand dollars, to keep her son in a private sanatorium which professes to cure epilepsy. One sad case is of a young woman who had been entirely self-supporting until five years ago, when epilepsy developed. She is alone in the world, she cannot secure work, and the only haven for her is either the dreaded almshouse or a hospital for the insane. One patient has been well educated, and has held and lost many positions because of his "spells," though he has not had more than two in four years. His trouble is in some way always discovered, and employers are unwilling to employ him because of the high rate of insurance called for by the "Workmen's Compensation Act." In almost every instance there is great financial need, and the families would have a hard fight even without the added burden of the afflicted son or daughter.

Many of the people are pathetically ignorant. For instance, the mother of four epileptic children stated that some enemy had put a "spell" on her. She spent much needed money on "herb doctors" and on a "colored lady who can take spells off." Another woman, the mother of a deaf and dumb and epileptic girl, will allow her to marry "if some nice deaf and dumb man, who can understand her and sympathize with her, comes along."

The only provision now made for the care of epileptics is for a few children (I have been able to have admitted but two in one and a half years) in the Rosewood Training School for Feeble-minded Children, the state hospitals for the insane, and the Silver Cross Home which is supported by The International Order of the King's Daughters and Sons. This latter home is the only one in Maryland solely for epileptics. It receives only women and girls and can accommodate but 25. I have been unable to secure a single admission there since January, 1914.

In order to send a patient to a state hospital, he must be examined and declared insane by two physicians. A large percentage of epileptics are not insane, and their families object to having them sent to state hospitals for the insane.

Maryland could fill to overflowing in a short time any good colony planned for epileptics. If there are 173 cases in one clinic of our dispensary, think of the number there must be throughout the city and the state, who are being treated at other dispensaries and by private physicians!

SUMMARY OF A REPORT OF SIXTY-FOUR CASES OF EPILEPSY IN PATIENTS FROM FOURTEEN YEARS TO FORTY YEARS OF AGE.

		Age—				Married	Unmarried
		14 to 20	20 to 30	30 to 40	40 to 50		
Number of	Males	31	13	15	3	6	25
	Females	28	8	12	8	5	23
Number of	Males	3	1	1	1	1	2
	Females	2	2	2
		64	64	24	28	12	52

AGE AT ONSET.

Under 12 years.....	41
From 12 to 20 years.....	21
Over 20 years.....	2
	64

WORK RECORD.

Have never worked.....	20
Have tried everything from errand boy to foreman in clothing shop	44
	64

Of the 44 who started work:

Gave up after a very short time.....	29
Remained at work.....	15
	44

EDUCATION.

Number attending public schools.....	38
Number attending parochial schools.....	19
Number never in school.....	7
	64

GRADE REACHED BEFORE LEAVING SCHOOL.

Left in first grade.....	5
" " second grade	1
" " third grade	5
" " fourth grade	15
" " fifth grade	8
" " sixth grade	9
" " seventh grade	7
" " eighth grade	5
" " first year of college.....	1
Unclassified	1
	57

REASONS FOR LEAVING SCHOOL.

Because of "spells".....	30
To work	27
	57

SALARY RECORD OF THE FIFTEEN WHO REMAINED AT WORK.

	Wage per week at beginning.	Wage per week at present time.	
1	\$2.50	\$6.00	} Increase 11
1	3.50	12.00	
1	3.50	12.00	
1	3.50	15.00	
1	3.50	8.50	
1	4.25	10.00	
1	1.25	6.00	
1	2.50	10.00	
1	2.50	9.00	
1	3.00	10.00	
1	1.50	11.00	} Decrease 1
1	2.50	1.50	
1	4.00	4.00	
1	3.50	3.50	
1	3.50	3.50	
			} Same 3

MENTAL STATE.

Very poor	38
Fair	17
Apparently normal	9
	64
Plainly institutional cases.....	38
Have had to ask help of some registered social agency.....	17

SEVERE ANEMIA WITH EOSINOPHILIA.*

By ARTHUR F. BEIFELD, M. D.,

AND

MILFORD E. BARNES, M. D., Chicago.

The facts pertinent to a discussion of the case forming the basis of this report are briefly as follows: The patient, a German of 68 years, entered the County Hospital, Chicago, November 27, 1915. His request upon admission was to be relieved of body vermin and to be given shelter. The noteworthy feature of the physical examination was the high-grade pediculosis corporis with its typically located scratch marks. The skin, especially of the trunk and extremities, was of a dark brown color, while in texture it was thick and harsh, suggesting an eczematous change superimposed upon the parasitic. The case was characteristically one of vagabond's disease. Contrasting with the blackish-brown pigmentation of the trunk were the lemon-yellow color of the face and the pallor of the visible mucous membranes.

A marked pulmonary emphysema with the usual associated findings was also present. Pulse, temperature and respirations were approximately normal while the patient was under observation. The systolic blood-pressure registered 110 mm., the diastolic 68. The ophthalmological examination presented no abnormalities aside from a bilateral cataract. The subcutaneous tissue was fairly well preserved. Asthenia, however, was marked and of a degree to keep the man confined to his bed throughout his stay in the institution. The nervous system showed no anomalies except a questionable Babinski phenomenon on the left side.

The cerebrospinal fluid exhibited a normal cellular content and negative globulin and Wassermann reactions. The latter was also negative in the blood. The urine on one examination contained a small amount of albumin but no casts, and on another no albumin but a few hyalin and granular casts. Blood cultures remained sterile.

A progressive weakness marked the course of the condition, exitus occurring January 28, 1916, just two months from the date of entrance. The final days of the illness revealed no new symptoms, death being due evidently to the asthenia.

The hematological findings are summarized in the following table.

The identity of the eosinophiles was unmistakable. The majority were of the size of a polymorphonuclear neutrophilic leucocyte, the remainder being somewhat larger. The nuclei, consisting generally of two round or oval segments united by a delicate chromatin bridge, did not stain as deeply as did those of the polynuclears. The large round granules, which in the fresh specimen stood out as highly refractile bodies, in the stained preparation varied in color from an almost crimson red through a pale red to a bluish red. While some of these cells were compactly filled with the granules, others contained

fewer, and still others showed clear round spaces formerly occupied by the acidophilic bodies.

The erythrocytic side of the blood-picture is embryonal, such as is characteristically met with in pernicious anemia. Thus, indicative of this type of erythropoiesis, are the many abnormally large cells, the high color-index and the presence of megaloblasts (without normoblasts). The leucocytic torpidity which constitutes so integral a feature of pernicious anemia—except in the remissions and in the presence of complicating infections—is evidenced here by the leucopenia and the relative lymphocytosis (in the later counts). The platelet diminution is also suggestive.

Utterly inconsistent, however, with pernicious anemia is the enormous eosinophilia. The following data may be cited relative to this point: Cabot,¹ in 52 cases, in which a total of 78

	Nov. 27, 1915.	Nov. 29, 1915.	Dec. 8, 1915.	Dec. 11, 1915.	Jan. 1, 1916.
Erythrocytes.....	1,667,000	1,670,000	1,440,000	1,600,000
Hemoglobin.....	36 (Duke)	36 (Sabin)	28 (Sabin)	34 (Sabin)
Color Index.....	1.44	1	1.3+
"Macrocytosis".....
Microcytosis.....
Polychromasia.....	++
Polychromatophilic.....	+
Basophilic Granules.....	+
Megaloblasts.....	1 per 1000	2 per 1000	1 per 1000
Normoblasts.....
Leucocytes.....	5000	5000	4200	5000
Polynuclear Neutrophils.....	33%	30%	34%	16%
Lymphocytes.....	13%	16%	14%	31%	16%
Large Mononuclears.....
Transitional.....	7%	11%	10%	1.7%	10%
Eosinophiles.....	17%	5%	10%	10%	2.7%
Basophiles.....	0%	0%	0%	0%	0%
Myelocytes.....	0%	0%	1%	0%	0%
Myeloblasts.....	0%	0%	0%	2.7%	0%
Irritant Forms.....	0%	0%	0%	0.5%	0%
Platelets.....	Practically absent	Much diminished

*Many giant-erythrocytes.

examinations were made, found an average eosinophilic count of 2.7 per cent. His highest figures were 9 per cent in one case and 6.6 per cent in another. Da Costa² obtained an average of 1.68 per cent in 31 cases, the highest counts being 5.2 per cent, 7.2 per cent and 8 per cent. In a collection of 1200 cases gathered from American and foreign sources, Cabot³ noted that the eosinophilic percentage was usually normal. In 83 out of 380 cases, however, it was above 7 per cent at some time during the course of the disease. Further, according to the same observer, the cells in question are subject to rather marked and rapid numerical variations from causes unknown.

Nægeli,⁴ Grawitz,⁵ Ehrlich and Lazarus⁶—in fact, hematologists generally—record similar observations, *i. e.*, that the eosinophilic white cells are usually not far from the normal relatively, though often they are reduced and not infrequently absent altogether in the periods of greatest marrow exhaustion. A persistent leukopoietic myeloid overactivity—polynuclear

* Read before the Chicago Society of Internal Medicine, January 24, 1916.

leucocytosis, myelocytosis, eosinophilia—is entirely at variance with the present-day conception of the nature of pernicious anemia.

The blood-picture of the essential, Addison-Biermer, type of pernicious anemia is indistinguishable from that produced by three known causes—helminthiasis, notably *dibothriocephalus latus*, syphilis and pregnancy. The possibility of the presence of an intestinal parasite was especially to be considered in this case because of the eosinophilia, though it is generally conceded that when the blood approaches the pernicious picture these cells behave as they do in the idiopathic form. Repeated examinations of the stools for ova, with employment of the Yaoita¹ antiformin method for rendering them more accessible, were uniformly negative. The negative Wassermann reaction both in the blood and cerebrospinal fluid made the presence of lues improbable. Trichiniasis, it may be noted parenthetically, entered into the differential diagnosis only as a possible cause of the eosinophilia, but not of the embryonal type of anemia; and a section of muscle from the biceps tendon revealed no trichinellæ.

There is another group of conditions which may produce a blood-picture similar in most respects to that of the Addison-Biermer type. These are the so-called secondary forms of pernicious anemia. It is not within the province of this paper to enter into the still unsettled question as to whether the idiopathic form exhibits hematological features by means of which it can generally be distinguished from the cases of known etiology. Be this as it may, the two are not infrequently difficult of differentiation. Malignancy, especially carcinoma of the stomach, hepatic affections, ulcerative endocarditis, inanition due to severe digestive disturbances, nephritis, chronic malaria, lead-poisoning, tumors of the bone-marrow, hemolytic icterus—these are the principal causes of severe anemias resembling the essential pernicious form.

Neither the anamnesis nor the physical or laboratory findings in the case furnished even a plausible basis for the diagnosis of any of the above-mentioned conditions. However, the relationship of malignancy to eosinophilia and of gastric carcinoma to pernicious-like blood-pictures made the study of the stomach especially interesting. Motility was good; in fact, as shown by the fluoroscopic examination, the pylorus was abnormally patent, allowing the barium meal to hurry through the organ. This we attributed to the associated achlorhydria, which often, as is well known, tends to produce an atonic pyloric sphincter. The Ewald meal, removed in an hour, yielded 100 cc. The X-ray plates showed no incompleteness of the gastric contour indicative of ulceration. Neither the stomach-contents nor the stools contained blood.

The essence of the case resides in the difficulty of reconciling the enormous eosinophilia with the leucocytic torpor (leucopenia, lymphocytosis), on the one hand, and with the blood-picture of pernicious anemia on the other. Two common causes of an increase in the acidophilic cells, though ordinarily associated with a normal total white-corpusele count, are obvious, *viz.*, the pulmonary emphysema, which in this regard

differs only in degree from bronchial asthma, and the dermatosis, which may cause an eosinophilia of 50 per cent or even higher. Neither of these conditions in itself, however, can be adduced in explanation of the embryonal type of anemia.

As an autopsy was not obtainable, theory must take the place of fact. The erythropoiesis is that of pernicious anemia, with which are harmonious also the leucopenia and the lymphocytosis. To explain the eosinophilia, however, if the case was actually one of pernicious anemia, one must assume either that the medullary tissues produced the eosinophilic cells in response to a selective stimulation, or that these cells were formed in extramedullary sites. In either case, the eczema (pediculosis) or the emphysema, or both, probably furnished the exciting cause of the eosinophilia.

While it is more or less generally agreed that the eosinophilic leucocytes may arise, under unusual conditions, outside of the bone marrow, there is a considerable difference of opinion as to the nature of such *histogenic foci*. Naegeli,² for example, believes that, if eosinophiles arise in the skin and mucous membranes—as is urged by some—they originate then only from myeloid tissue which has appeared at new points, that is, perivascularly, as in embryonic life, and that in such new areas of myeloid tissue there are always, in addition, eosinophilic myelocytes and myeloid elements other than the eosinophilic. Illustrative of this are Hoffmann's³ findings in a case of mercurial dermatitis, in which he noted in the greatly inflamed cutis a marked dilation of the papillary and subpapillary vessels, with swelling and cloudiness of the endothelium, and a rich perivascular round-cell infiltration containing many eosinophiles. Further, in sections of the vessels of the rete, and in the exudate of the horny layer, were many eosinophiles and also some mononuclear (myelocytic) forms. On the basis of this picture, Hoffmann came to the conclusion that the skin was a workshop for eosinophiles under pathological conditions.

On the other side there are those like Dominici⁴ and Weidenreich,⁵ who maintain that the eosinophiles may arise locally from the tissues involved in the particular case, not from metastatic medullary foci, but from lymphocytes, without an intermediate stage such as the myelocyte. In this case the eosinophilic granules are presumed to originate from disintegrated hemoglobin, a view especially championed by Weidenreich.⁶ Though these conceptions apparently have little in their favor, they harmonize well with certain conditions present in our case. Thus, the eosinophiles have been most numerous at the times when the lymphocytes were relatively few. Furthermore, as pointed out by Weidenreich, the eosinophiles are likely to be increased when there is a diminution in the erythrocytes and evidence of an augmented destruction of the red cells.

Despite our inability to obtain an autopsy in this case, it has seemed worthy of being placed on record because of its one outstanding feature, *viz.*, the association of an embryonal type of erythropoiesis, plus leucopenia and relative lymphocytosis, with an enormous eosinophilia. To reconcile the latter with

the idiopathic form of pernicious anemia one must assume either a selective—and highly anomalous—stimulation of the bone-marrow, or an extramedullary origin of the eosinophilic cells. The assumption of a secondary pernicious anemia, so-called, due in this case to an undiscovered cause, is scarcely more satisfactory, in that cases with a discoverable etiology differ in one or more particulars—normal or increased leucocyte count, post-embryonal erythropoiesis, a color-index hovering about one or even less than one, etc.—from the hematological picture tabulated above; and, furthermore, as already noted, it is generally true that in severe secondary anemias produced by conditions which likewise give rise to an eosinophilia, the latter tends to recede, the acidophilic cells progressively diminishing, as the blood-picture approaches that of the idiopathic type.

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THE POSSIBLE RÔLE OF BOOKS IN THE DISSEMINATION OF THE CONTAGIOUS DISEASES.

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From the public health standpoint books which have come in contact with patients suffering from the communicable or the contagious diseases are always likely to be considered factors in the spread of such diseases. Many individuals, in fact, attribute attacks of such infections as diphtheria to the handling of books previously used by individuals suffering from diphtheria, but in no instance has this relationship ever been satisfactorily demonstrated by the isolation of the diphtheria bacillus from this source. Despite this fact, current popular literature is full of references to this mode of infection. In many instances, however, as in the classical case described by Bugbee,¹ there is no satisfactory evidence that diphtheria was carried in this way. Nevertheless, the possibility that books may convey disease and the belief of the lay public in this possibility is of sufficient importance to merit an investigation of this problem along laboratory lines.

Before considering the detailed experiments it may be wise to consider the general subject of the isolation of pathogenic bacteria, such as diphtheria bacilli, from inanimate objects. Thus, Trevelyan² cultivated diphtheria bacilli from a handkerchief 11 weeks after it had been used by a child suffering from diphtheria. Wright and Emerson³ cultivated virulent diphtheria bacilli from a brush used in sweeping a ward in which several diphtheria patients had been cared for. They also isolated the same organism from the dust clinging to the shoes of the nurses in charge of the same ward, and an organism, said to be the diphtheria bacillus but lacking in virulence, was found on the hair of one of these nurses. Wenghardt⁴ was able to isolate diphtheria bacilli from various objects handled by a patient with diphtheria, such as a neck-cloth and a bottle, and he also obtained the organism from a spot on the carpet about 0.5 m. distant from the patient. Hill⁵ succeeded in

isolating non-virulent diphtheria bacilli from a toy and from a handkerchief used by a patient after release from isolation. He also made a very extensive search for diphtheria bacilli on other inanimate objects, which had come in contact with patients suffering from diphtheria, without, however, any positive results. His examinations were made within a comparatively short time after the possible infection (within eight days), and the objects he examined had been very closely handled by the patient.

It is seen from this résumé that apparently, at times, the diphtheria bacillus may cling to inanimate objects after they have once become infected by the discharges of the diphtheria patient, but that the findings are of such variance as to indicate that the organisms of diphtheria do not find a nidus for development on objects of this character. It becomes a matter of importance, therefore, to determine, first, whether books that have come in contact with children suffering from infectious diseases are capable of harboring any organism with pathogenic properties. With this end in view, we have made a careful examination of some 75 books obtained from the Enoch Pratt Library in Baltimore (Branch 13), in the hopes of answering this question. These books had been in constant circulation for several years among children in whose homes sanitary conditions were decidedly unsatisfactory, and were badly soiled and torn. The books were swabbed off with sterile cotton swabs and the swabs then thoroughly shaken into sterile fluid, either broth or salt solution, which was then plated on ordinary media. The swabs were also rubbed over the surface of special media used in the isolation of diphtheria bacillus, such as Loeffler's blood serum and Conradi and Troch's⁶ telluride medium. Finally, the broth or salt solutions in which the swabs had been placed originally were

centrifugized and the sediment was used for inoculation into animals. The results of this examination may be summarized briefly as follows: The majority of bacteria found on books belonged to the chromogenic group, corresponding to the species usually found in atmospheric air. They were in general, however, somewhat attenuated, and pronounced pigment production often did not come out until after prolonged cultivation in the laboratory. In addition to the chromogenic organisms, non-chromogenic micrococci and bacilli were not infrequent. They also can be identified as forms found in the atmosphere, such as *Micrococcus cremoides*, *Bacillus proteus zenkeri* and *Bact. troilli* (*Bacterium lactis longum* b.). Spore-bearing bacteria were often more abundant than the chromogens, the types found being the same as those isolated from dust and described in another place.⁷ Finally, a few of the ordinary forms of hyphomycetes, chiefly the actinomycetes, were occasionally noticed, but never any of the basidiomycetes. In two instances the presumptive test for the colon bacillus was positive, and this organism was found subsequently in pure culture. The findings of Winslow,⁸ who has shown that the colon bacillus may be obtained from the hands of school children, are of interest in this connection, and the relative infrequency of this organism on soiled books would seem to indicate that it does not find on books the proper conditions for multiplication. Nevertheless, our positive findings are suggestive, in view of the fact that the viability of the colon bacillus is not very different from that of the typhoid bacillus. In no instance could the diphtheria bacillus be isolated from these books, either by the use of special media or of animal inoculation, although we were able to prove that some of the books in the lot examined had come from homes where children were suffering from the disease.

We then undertook the study of schoolbooks in the homes of diphtheria patients, and through the kindness of Dr. N. Gorter, Health Commissioner of Baltimore, it was possible to collect schoolbooks from 50 houses where diphtheria had existed, the diagnoses having been established clinically and culturally. Only those books were selected for examination where there was definite evidence that they had been handled by the patient during the disease. Altogether 150 books were studied, both by cultural methods and by animal inoculation, and our results were entirely negative. The belief that books assist in the dissemination of this disease, therefore, in our opinion, received no substantial support from their bacteriological examination in the laboratory.*

The attempt was next made to determine experimentally how long various well-established species of bacteria are able

to survive on books, by deliberately contaminating them and taking cultures at various intervals. It had been previously shown by Billings and Peckham that they were able to recover *B. coli* from a silk thread that had been kept in a dark cupboard for 152 days. They also found that both *B. coli* and *B. typhosus*, when plated on agar plates and exposed to direct sunlight, show a decrease of 98 per cent within two hours, but no appreciable decrease after two days when exposed to diffuse daylight. In our experiments with these and other organisms the books were first sterilized with steam under pressure and then the covers and pages were thoroughly rubbed over with cotton swabs saturated with broth suspensions of the organism. The books were then placed aside and retained in various conditions, some in diffuse daylight, others in the dark at room temperature; they were also exposed to low temperatures and direct sunlight. As can be seen from the following table,

TABLE I. (*B. coli*.)

Condition.	Part of Book.	Average period of survival.
Dry, no daylight, room temp.	Int.	5 to 6 mos.
Dry, no daylight, room temp.	Ext.	3 to 4 mos.
Moist, no daylight, room temp.	Int.	5 to 6 mos.
Moist, no daylight, room temp.	Ext.	5 to 6 mos.
Dry, diffuse daylight, room temp.	Int.	4 to 5 mos.
Dry, diffuse daylight, room temp.	Ext.	1 to 2 mos.
Moist, diffuse daylight, room temp.	Int.	4 to 5 mos.
Moist, diffuse daylight, room temp.	Ext.	2 to 3 mos.
Low temperature (ice-box)	Int.	2 mos.
No daylight	Ext.	1 mo.
Direct sunlight (temp. 34° C.)	Ext.	12 to 20 hrs.

B. coli could be recovered from these books after so long a period as five or six months, when the conditions were proper for their survival. In other instances the organism apparently died out within a comparatively short period of three or four weeks. It is significant that they were rapidly destroyed by direct sunlight, the organisms not being recovered after 20 hours. In our experiments we recovered *B. coli* up to the period of 20 hours, after which time the organisms did not grow on our plates. Billings and Peckham¹⁰ found that under the influence of direct sunlight a marked decrease of the organisms occurred within two hours. It is possible, as Billings and Peckham suggest, that direct sunlight not only destroys the micro-organisms, but also affects culture media so as to render them unsuitable for bacterial development.

The viability of the typhoid bacillus has been investigated by a number of individuals, and the opinion is usually held that this organism and *B. coli* succumb to the same deleterious influences. Thus, Besson¹¹ states that *B. typhosus* is killed by exposure to direct sunlight (in the month of May) within from four to eight hours. Vincent found that the typhoid bacillus, when spread on ordinary cloth and exposed to direct sunlight, was destroyed within from nine to 26 hours. J. McFarland¹² found that the typhoid bacillus would survive on linen for as long a period as 60 or 75 days, and upon buckskin for from 80 to 85 days, when both fabrics were kept under ordinary conditions. As can be seen from the following table,

* Similar procedures were made use of in regard to books that had come in contact with patients suffering from tuberculosis. The number of books examined was relatively small and the negative findings may not be considered sufficiently conclusive. Kenwood and Dove⁹ carried on a large number of experiments as to risks from tuberculous infection retained in books and arrived at the following conclusion:

"There is probably no material risk involved in the reissue of books recently read by consumptives, unless the books are obviously soiled. Even then the risks are very slight."

TABLE II. (*B. typhosus*.)

Condition.	Part of Book.	Average period of survival.
Dry, no daylight, room temp.	Ext.	20 days.
Dry, no daylight, room temp.	Int.	4 to 5 mos.
Moist, no daylight, room temp.	Ext.	10 days.
Moist, no daylight, room temp.	Int.	3 to 4 mos.
Dry, diffuse daylight, room temp.	Ext.	12 days.
Dry, diffuse daylight, room temp.	Int.	3 mos.
Moist, diffuse daylight, room temp.	Ext.	10 days.
Moist, diffuse daylight, room temp.	Int.	3 to 4 mos.
Low temperature (ice-box)	Int.	2 to 3 mos.
Low temperature (ice-box)	Ext.	3 to 4 mos.
Direct sunlight (temp. 32° C.)	Ext.	12 to 20 hrs.

when this is compared with the preceding table, the colon bacillus apparently survives for a longer period of time than the typhoid bacillus, when the two organisms are placed upon books under apparently identical conditions. This may be explained by the relative resistance of *B. coli* to greater degrees of dryness and moisture than is exhibited by the typhoid bacillus. Apparently also the typhoid bacillus is more rapidly destroyed by diffuse daylight than the colon bacillus, while both organisms are destroyed in a comparatively short time by exposure to direct sunlight. Finally, it is quite evident that both *B. coli* and *B. typhosus* are able to survive for so long a time upon books kept under certain conditions, as to suggest the possibility that books may serve as vehicles of infection in typhoid fever.

In a disease so important as diphtheria it is natural to expect that the resistance of the infective organism to various conditions should have been tested with great care. Thus, we find that Hill⁵ has estimated the resistance of the diphtheria bacillus to diffuse daylight and has found that the organisms survived at times for as long a period as 20 days, whereas at other times they were not alive after seven days at room temperature. Abel¹² found that the diphtheria bacilli could be recovered alive from silk threads kept at room temperature and low temperature (in the dark) for as long a period as 86 days and, what is still more important, that their virulence had not lessened during this period of time. Deycke¹³ found that diphtheria bacilli dried on lime-wash, oil, paint, and glue spread on wood and cement survived for various periods from one to 18 days. Reyes¹⁴ compared the resistance of *B. diphtheriae*, when placed on silk paper, linen, mud and sand, subjected to diffuse daylight at times and at other times kept in the dark under varying conditions of moisture. The longest period of time during which the organisms survived at all was in mud under moist conditions, from which he isolated the organism after three months. Paper contaminated with the bacteria and kept in a dry condition in the dark showed the organism after four days only, but when kept in a moist condition showed the organism after eight days. Kept in the light in a dry condition the organism survived on paper for 36 days, but for 56 days in the moist condition. Germano¹⁵ concluded from his experiments that diphtheria bacilli can survive for a long period of time on ordinary cloth, at once suggesting the danger that may arise when schoolbooks are provided with cloth covers. Finally, Gehrke¹⁶ found that the diphtheria bacillus, when suspended in water, was killed by

direct sunlight in from two to eight hours, while Ledoux¹⁷ demonstrated that the organisms, when dried in thin layers, were rapidly destroyed by the same agency.

In our experiments with this organism we employed recently isolated strains of a highly virulent character, and that killed guinea-pigs weighing 250 gm. within 48 hours. As can be seen from the following table, in certain instances the organ-

TABLE III. (*B. diphtheriae*.)

Condition.	Part of Book.	Average period of survival.
Dry, no daylight, room temp.	Int.	2 to 3 mos.
Dry, no daylight, room temp.	Ext.	1 mo.
Moist, no daylight, room temp.	Int.	1 to 2 mos.
Moist, no daylight, room temp.	Ext.	22 days.
Dry, diffuse daylight, room temp.	Int.	2 to 3 mos.
Dry, diffuse daylight, room temp.	Ext.	5 days.
Moist, diffuse daylight, room temp.	Int.	1 to 2 mos.
Moist, diffuse daylight, room temp.	Ext.	1 to 2 days.
Low temperature (ice-box, no daylight) . Int.		1 mo.
Low temperature (ice-box, no daylight) . Ext.		20 days.
Direct sunlight (temp. 35° C.)	Ext.	4 to 6 hrs.

isms survived for a period of three months on books, and in these experiments the virulence of the organism remained practically undiminished. In general the exposure of the books to diffuse daylight was fairly efficient for the destruction of the organisms upon the exterior, but very much less efficient for the destruction of the bacteria inside the covers. The most favorable conditions for survival of the organisms are moisture, lack of sunlight, and room temperature.

Finally, the organisms were destroyed by direct sunlight by an exposure of but four to six hours.

CONCLUSIONS.

From the experiments described in this paper, which we may say have been repeated on a number of occasions, one or two points of considerable importance come out.

1. Pathogenic bacteria can seldom be isolated from books which have been handled by sick patients, and there is, therefore, no empirical reason for maintaining that books serve as vehicles of infection.

2. Direct sunlight and diffuse daylight are the most efficient germicides for organisms found on books, as they are for the same organisms under other conditions.

3. The fact that pathogenic bacteria, like the typhoid bacillus and diphtheria bacillus, can be recovered from artificially infected books under various circumstances after long periods of time, and the fact that the diphtheria bacillus does not lose in virulence during this period, are a sufficient reason for insisting upon the thorough disinfection of books which have been handled by patients.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

FEBRUARY 7, 1916.

1. Presentation of a Possible Case of Heat Cramps. R. L. HADEN.

This patient is an Austrian, 29 years old. He was admitted to the hospital on February 3, 1916, complaining of cramps. He has had no similar illness before, and his past history is unimportant. For the last three months he has worked at a copper mill, where he has been filling the furnaces in which the copper and zinc are smelted. He says that he has worked in many hot places, including the furnace room of a trans-Atlantic liner, but that this is the hottest place he has ever been in.

He has been working on the night shift. He went to work on Wednesday at 4 p. m., after eating a light dinner. At 8 p. m. he drank some coffee and after this did not eat or drink anything. About 10 p. m. he began to have diarrhœa, which gradually increased in intensity until midnight, when he was having a stool every 5 or 10 minutes. The stools were copious and watery. He does not know whether they contained blood or mucus. The diarrhœa continued, though it was less severe, until 2 a. m., when he lay down near the furnace and went to sleep. Usually he had been sleeping outside. At 3 a. m. he awoke with intense abdominal cramps, which lasted only a few moments and were followed by severe cramps in the muscles of the legs, arms, neck and face. He also says that he was unable to speak. The cramps became less severe about noon. He vomited everything swallowed. The diarrhœa ceased soon after the onset of the cramps.

On admission to the hospital at 4 p. m. he looked very ill; he lay in bed with his eyes half closed; the cheeks were sunken; the lips and finger tips were quite cyanotic. At intervals there were localized tetanic contractions of the muscles of the legs, thighs, and arms. All the muscles of the body were very tender on palpation. The head, heart, and lungs were negative. The abdomen was scaphoid, but showed no peristalsis or abnormal masses. There was diffuse tenderness which seemed to be in the abdominal wall itself. He had no stools after admission and the muscle cramps ceased soon after the administration of morphin. He had no fever. The W. B. C. were 18,000. He has rapidly recovered.

DISCUSSION.

DR. JANEWAY: It seemed worth while to present this patient, although the diagnosis is not absolutely certain, in order to call attention to a disease rare in the literature, but apparently not so

rare in real life. Of course, in this particular patient, one may assume that he suffered from cholera nostras and that the muscle cramps were such as can occur in Asiatic cholera or some other choleraic diarrhœa. Against that is the fact that the diarrhœa stopped before the cramps began and that the patient did not show the extremely pinched look and the great prostration, feebleness of voice, etc., that go with cases of choleraic diarrhœa. Edsall described in 1904,¹ and subsequently in 1908,² a condition of extreme cramp-like contractions of all of the muscles of the body, occurring in individuals performing hard manual labor, while exposed to excessive temperature. The first two cases occurred during extremely hot weather, but the subsequent group of cases came from foundry workers exposed to the great heat of furnaces. On further study, he found that this condition was quite well known to ship's surgeons who dealt with stokers, and to some physicians in great industrial plants. With the exception of Edsall's article and a short publication by Meyers in the Virginia Medical Semi-Monthly, little has appeared about this condition. The subject is an interesting one and of considerable importance. A number of men die, as the result of these cramps, in the course of a few hours, or in a day or two. Dr. Edsall made a study of the metabolic changes, which he told me of, but I have not been able to find that he ever published his results. I am in hopes that the opportunity of seeing this patient may interest some of you who have access to patients from the big industrial plants, who are exposed to high temperatures, and that you may look out for the condition and perhaps describe it more fully, particularly with regard to what Edsall found—an enormous nitrogen output in the urine, with apparently complete retention of chlorides. Edsall was inclined to regard the condition as the immediate effect upon the muscle of the high temperature and the cramps as resulting directly from actual changes within the muscle substance. The similarity of the cramps to those of choleraic diarrhœa would bring up the question whether desiccation from excessive perspiration may play a part. In this particular patient, I am inclined to think that the diarrhœa predisposed him to the development of heat cramps, though one may believe that he had merely an extremely severe type of muscle cramps in connection with a short attack of cholera nostras. The patient had no rise of temperature.

¹ Edsall, D. L.: Two cases of Violent but Transitory Myokymia and Myotonia, apparently due to excessive hot weather. Am. Jour. Med. Sci., 1904, n. s., CXXVIII, 1003-1011.

² A Disorder due to Exposure to Intense Heat. J. A. M. A., 1908, LI, 1969.

2. The Diagnosis and Treatment of Umbilical Concretions, with Report of a Case. DR. S. V. IRWIN.

Abscesses of the umbilicus are not common and, of those that are met with, the larger percentage are due to concretions. In over 108,000 admissions to The Johns Hopkins Hospital, in all services, only three cases of abscess of the umbilicus have been observed. Two of these were certainly due to concretions, and although there may be some doubt about the third case, after having made a careful analysis of the history, I have been led to believe that in this also the abscess was due to a concretion.

The case which I am presenting to you this evening is that of an unmarried girl, about 18 years of age, who entered the hospital January 6, 1916, complaining of a very painful, indurated and tender umbilicus which had been discharging pus for nine weeks.

Family History.—Unimportant.

Previous History.—Her general health was always good until an attack of measles five years previously—since which time she has suffered with frequent headaches and weakness. During the last nine months she has had attacks of fainting, often preceded by vertigo. She had slight attacks of otitis media six months ago. She has had occasional slight attacks of palpitation of the heart and edema of the ankles. Her appetite has been poor during the last six months. During this time she has had a few attacks of very slight hematemesis—also occasional attacks of pain in the right lower abdominal quadrant. She gives a rather uncertain history of tarry stools. She has had a tendency to constipation.

She has had various slight attacks of cystitis that always cleared up rapidly under treatment. One year ago she had an attack of metrorrhagia, which persisted for eight months, until a curettage was done; since this time menstruation has been regular. She has lost about 25 pounds in weight during the last three months.

Present Illness.—On August 15, 1915, five months before admission, the patient was seized with a sudden severe pain in the right lower abdominal quadrant, followed by nausea and vomiting. On the next day a burning sensation was felt just to the left of the umbilicus, followed two days later by a slight swelling in this region, which grew larger and more painful until it reached the size of a hen's egg. The mass was fluctuant and surrounded by a ring of induration, but without any noticeable reddening. On October 23, the mass ruptured and a bloody, foul-smelling, purulent material was discharged from the umbilicus. After this the pain was somewhat lessened, but the bloody material continued to discharge for about three weeks. It then ceased for a week, but the tissues around the umbilicus became indurated, tender, and reddened; the swelling became so great that the umbilicus was almost obliterated. Finally, a sero-purulent material, which soon became thick, creamy, and greenish in character, began to discharge from the now obscured umbilicus, and the pain changed from that of a sharp stabbing character to one of a burning stinging nature.

The physical examination was practically negative, except for the abdomen. At the umbilicus there was an ulcerated area, about 5 cm. in diameter, crusty, reddish-yellow, scab-like in character, which was immediately surrounded by an indurated area extending 3 cm. outside of the scaly zone. The abdomen was everywhere extremely sensitive, the lightest palpation causing the patient to cringe with pain. This was more marked as one approached the umbilicus. There was no muscle spasm. The leucocytes were 8,440; the hæmoglobin was 83%. The pus from umbilicus showed many cocci which were gram-negative. The urine was normal. The pus on repeated examinations gave a negative guaiac test. Dr. Thomas S. Cullen diagnosed the case as one of umbilical concretion.

Umbilical concretions are found most often in people of middle age; rarely in children or the aged. People of unclean habits are most frequently affected, particularly the men, probably due to the fact that they lead a more active life.

The first symptom noticed is an attack of severe pain, usually referred to the umbilical region. Nothing is seen for from one to three days later, when a swelling, which is often surrounded by a reddened zone, appears at or near the umbilicus. The pain continues, being intensified by anything which causes the slightest tension on the abdominal muscles. Induration, usually accompanied by a reddening of the overlying skin, spreads through the tissues in the immediate neighborhood of the umbilicus, causing it to assume the appearance of a fistulous opening and to become exquisitely tender and painful. The induration increases and is usually uniform, but at times an elevation, varying in size from a pea to a hen's egg, may be produced, which later may become soft and fluctuant at its center. The patient suddenly experiences in the umbilicus an excruciating pain, which is followed almost immediately by a gush of bloody, purulent, often foul-smelling material, after which the pain markedly diminishes. The discharge in a few days changes to a serous character and later becomes thick and creamy-yellow, disappearing entirely in a short while if the foreign body has been extruded with the flow of pus; otherwise it continues until the obstruction is removed.

Most of the concretions are composed of a sebaceous material, which is exceedingly friable. They often contain hairs, bits of wool or cotton fibers, or even particles of stone, coal or wood, depending on the person's occupation. Besides these, there are concretions which have a pearly appearance and are firm, smooth, and laminated, varying in size from a pea to that of a large marble.

The factors of greatest etiological importance in the causation of umbilical concretions are:

1. Lack of personal cleanliness.
2. An unusually deep umbilicus.

Foreign particles, sweat or sebaceous material collecting in the umbilical depression may form a small ball, which by its constant irritation causes an exfoliation of the squamous epithelium lining the umbilicus. The resulting mass renders the neighboring subcutaneous fat or the peritoneal tissues susceptible to infection, with the consequent thickening and hardening of these tissues and narrowing of the umbilical opening until it becomes little larger than a fistulous aperture. Pus accumulates and dilates the depression, which finally becomes closed off and there is formed a large tense pus sac that presses on the neighboring, intensely inflamed tissue, producing an increase in the already severe pain and tenderness.

If the cavity of the umbilicus be dilated, it is usually found greatly distended, filled with pus, and containing a concretion of a solid or friable material. This cavity may be several centimeters in diameter; or sometimes two cavities may be found, the one, containing the pus, being connected by a short, narrow, fistulous tract with another smaller one, in which lies the concretion. Thorough exploration is, therefore, always necessary, as pus will continue to form as long as the foreign material remains.

The diagnosis of umbilical concretions is not always an easy task, since any condition which produces induration, swelling and tenderness, or a discharge of purulent material through the umbilicus, necessitates a consideration of all the various diseases which can produce such signs in this region.

Quite a number of cases of dermoid cyst of the umbilicus are on record. The majority of these, however, have not been dermoids, but have been abscesses due to an accumulation of cheesy material and hair in the umbilical depression.

Sub-umbilical abscesses occasionally occur. It has been found that, just below the umbilicus, there exists a space bounded in front by the recti muscles, and behind by the peritoneum; and, as

one passes backward from the linea alba, one will often find a partition, which divides the triangular sub-umbilical space into two cavities. This sub-umbilical space is occasionally the seat of an abscess.

Now and then urachal remains become infected, giving rise to an abscess between the umbilicus and symphysis. These infections are usually of a low grade; they occasionally give rise to an escape of pus from the umbilicus.

3. Medical Aspects of the European War. (Abstract.) DR. A. M. FAUNTLEROY, U. S. N.

Dr. Fauntleroy gave a very interesting account of the methods used in France in the care of the wounded. He showed a number of lantern slides, illustrating the first aid stations, where the tetanus and antitoxin vaccines are administered, the field hospitals and the base hospitals. Another group of pictures showed the use made of railway stations as first aid hospitals, before the wounded are transported to the base hospitals.

In an interesting series of pictures he showed the types of military ambulances in use; also the motor field hospital, which consists of several machines carrying x-ray and sterilizing equipment, and materials for a portable operating room. Apparently, this form of hospital has been used with much success.

Some time was devoted to a consideration of the splendid work done at the American Ambulance in Paris, from the clinical and also from the laboratory side. The results of treatment seemed to be remarkably good. A good deal of the apparatus used for the orthopedic cases was specially devised and made in the orthopedic workshop of the American Ambulance, and met the needs most successfully.

Dr. Fauntleroy did not go into detail with regard to the treatment of infected wounds, calling on Dr. Kenneth Taylor to present this aspect of the work.

4. Wound Infection and Treatment. (Abstract.) DR. KENNETH TAYLOR.

I would like to emphasize the points that the wounds are heavily infected and are infected by three distinct organisms, which are the cause of most of the deaths from infection as we see them in the hospitals. First, the tetanus bacillus, which has been practically eliminated, so far as the French army is concerned, by the systematic use of antitoxin, which, as Dr. Fauntleroy has said, is usually given at the first aid station, and, if not there, at the first hospital the patient comes to. Second, the streptococcus is still one of the agents that kills most of the men from wound infection. The third, and perhaps the one you are most interested in here, first described by Dr. Welch, is *B. aerogenes capsulatus*, which has become one of the most active factors. It occurs in from 70-80 per cent of the fresh wounds, and persists for varying periods of time, sometimes as long as 100 days after the injury, in chronic sinuses. By gas gangrene, we mean the death of greater or lesser extents of muscle tissue, due, we think, to local infection and the local elaboration of gas and some toxic principle by this bacillus.

The condition is associated with a swelling involving the muscles opening into the wound, a heavy, sweetish odor, the presence of gas either beneath the skin or bubbling from the wound, discoloration and edema of the skin and subcutaneous emphysema with or without blebs. Nearly 70 per cent of our fresh wounds showed this organism. Indeed it has been found to be so common that we have come to regard our fresh wounds as cases of potential gas gangrene. It is the one thing every surgeon is on the lookout for in the early stages of the wounds. It occurs rapidly. A fairly innocent wound will assume large proportions, distension will occur, and the whole course may be very rapid.

In regard to the incidence of the organism, we found in one series of cases, in wounds which were ten or more days old,

an incidence of 65 per cent. In another series there was an incidence of 70 per cent. In about 28 per cent of these, or slightly more than one-fourth, the diagnosis of gas gangrene was made independently of the laboratory. All the symptoms were present. At the American Ambulance gas gangrene has furnished slightly over 10 per cent of the fatal cases during the year I was at the hospital. A great many other cases have resulted in the loss of a limb, and in many instances it has undoubtedly been an accessory factor.

After watching the cases in the hospital, examining the specimens from the mortuary and the cadaver, together with more or less extensive animal experiments, we have considered that the more severe or fatal cases pass through certain definite stages. We have the *treatment stage*, which represents the stage in which there is local infection of the wound, with perhaps gas bubbles and smears showing the gas bacillus. Then we recognize the *stage of gas distension*, which we think is the result of some obstruction to the escape of the gas. The organism shows a preference for muscle tissue, and dead muscle is its favorite food. This obstruction causes a condition of gas distension. During this stage may be seen the swelling, subcutaneous edema and the discoloration of the skin, the edema perhaps being due to the intermuscular pressure, which is due to the distension by gas and the obstruction not only of the myelin, but also the vascular, circulation of the muscles. The third stage is the *explosive stage*, characterized by the rapid swelling of the muscles, associated with subcutaneous crepitus. The subcutaneous gas is probably the result of the rupture of muscle sheaths, and the rapid expansion of the gas probably aids in the dissemination of the bacillus, as the distribution of the gas is in direct relationship with the distribution of the bacilli or the extent of the infection. By experimenting on guinea-pigs, we have found that we can inject the thighs of a series of animals, kill them at intervals, and after a period of from 3 to 4 hours find a complete gas distension of a group of muscles; and yet, when the whole leg is dissected, we find that the bacteria are still limited practically to the point of implantation.

Following the rapid expansion of gas in the explosive stage, comes the *stage of systemic infection*, during which the individual is poisoned probably by two factors—a toxin or a toxic principle formed by the organism, and toxic by-products. The state of septicæmia is probably very rare, and is probably also a terminal condition.

I have seen one case in which the organism was recovered from the blood.

The first stage of local infection in the wound, with the free escape of gas, represents the common type, and most cases do not pass beyond this stage. When the free escape becomes interfered with, the stage of gas distension develops rapidly and passes, frequently within a few hours, into the third stage. The progress is tremendously rapid. I have seen men who wished to get up out of bed dead six hours later from gas gangrene.

Another special point is that the stage of gas distension may not be recognized, as it need not be painful. I suppose that a sort of pressure anesthesia is present. Often very sudden collapse occurs, which is evidently due to an acute toxæmia. If drainage sufficient for the escape of gas be established, recovery is usual. The possibility of gas embolism cannot be excluded. It is probably the principal cause of death.

This analysis has been based upon several observations. We have looked into the question of toxic principles formed by the organism, and found no active endotoxin. The toxic principle in 48-hour broths in which the bacteria have grown, but only in large doses, will kill guinea-pigs with symptoms closely resembling those of an active infection. The other factor is the gas. We have satisfied ourselves that this is not toxic. We have been able to remove the carbon dioxide, which forms about 40 per cent of it,

and have injected subcutaneously into the peritoneum of guinea-pigs large amounts of the remaining gas. While it is possible to blow a small guinea-pig up to the size of a toy balloon, the animal suffers little discomfort and there are no toxic symptoms.

The mechanical action is one of the chief factors in the infection. You can attach an indicator from a steam sterilizer, for instance, to a test tube of a medium inoculated with bacteria, and can run up a pressure of an atmosphere and a half in a few hours. The picture in the muscle reminds one of the same condition.

One of the chief problems in treatment has become that of establishing drainage for the escape of gas rather than for the escape of pus. This is a very difficult problem, as the gas extends by the process of muscle distension and infiltration. For the local treatment we have been using a quinine solution, a procedure which was based on experimental evidence and which has worked out fairly well clinically. In experimenting with a good many antiseptics, we found that quinine seemed to be most active, and especially hydrochinon. Carbolic acid is a poor antiseptic against the anaerobes and especially against the gas bacillus. In a favorable medium, the gas bacillus will grow in the presence of nearly 2.5 per cent of carbolic acid. Laboratory experiments have shown that we have been able to rid of gas bacillus wounds much earlier by the use of quinine than of the other antiseptics tried.

DISCUSSION.

DR. WELCH: It is very interesting to hear from both Dr. Fauntleroy and Dr. Taylor of the elimination of tetanus. This is one of the great triumphs of preventive medicine. The control of typhoid fever by vaccination is another great triumph. I understood Dr. Fauntleroy to say that the vaccine used in the French army is one that produces a severe reaction, but is very effective in the control of typhoid fever. I understand that this is not used for the para-typhoid fevers.

I have been much interested in Dr. Taylor's studies of the gas bacillus, which was first observed here and which has turned out to be of such importance in surgery. There has been a laboratory study of the organism from Dr. Rosenau's laboratory in Boston, made by Dr. Simmons. He has discussed a great many of the questions relating to the character of the organism. He takes the position that there are variations, and that possibly a group of these organisms exists. Of course we recognized here that this is one of the most widely distributed of pathogenic bacteria, appearing everywhere in soil and in the intestinal contents, not only in human beings but in most domestic animals. It is, therefore, not surprising to hear from Dr. Taylor that the organism is found in 71 per cent of the wounds examined bacteriologically. It is evident that fighting in the trenches brought about possibilities of contamination of the wound with soil that have never appeared before.

Experiments and observations have shown that the mere presence of the gas bacillus or the tetanus bacillus in the wound does not constitute infection, but that a variety of circumstances are necessary to cause this. What these are, we do not know altogether, but there must be favoring circumstances; for the presence of the bacteria, although essential to infection, does not insure infection.

This discovery of the value of the treatment of these wounds with quinine solutions is certainly a very valuable contribution. It is quite interesting and rather surprising that this drug should turn out to be so valuable a bactericidal for this particular organism.

FEBRUARY 21, 1916.

1. Nerve Conduction in the Non-Medullated Nerves of Medusa Cassiopea. (Abstract.) By ALFRED GOLDSBOROUGH MAYER.

If a pulsation wave be started in one direction in any circuit-shaped strip of tissue, it cannot escape from the circuit, but

must continue to move forward until stopped by a wave going in the other direction, blocked by a break in the circuit, or exhausted by fatigue. Such waves may continue for more than a week in ring-shaped strips of the sub-umbrella tissue of *Cassiopea*. The stimulus which produces this contraction is neurogenic, and, if external conditions such as salinity, temperature, CO_2 , and H-ion concentration, remain constant, its rate also remains practically constant. If, however, we dilute the sea water with distilled water, 0.9 molecular dextrose, or 0.4 molecular magnesium chloride, the rate declines. The formula for the decline when these solutions contain the same concentration of H- and OH-ions as the sea water is

$$y = 2.512 x^{0.4}$$

where y is the rate of nerve-conduction, and x is the concentration of the cations of sodium, calcium, and potassium in the surrounding sea water.

This formula resembles Freundlich's expression for chemical adsorption, and suggests that the sodium, calcium, and potassium cations that take part in nerve conduction are adsorbed, being attracted to the surfaces of the negatively charged colloidal particles of the nerve. Thus, being a chemical reaction, nerve-conduction must, by Wilhelmy's law, progress at a rate proportional to the concentration of the adsorbed sodium, calcium, and potassium cations which conduct it. Also, when these cations combine to form an ion-proteid, they leave unbalanced the negative charges upon the colloidal particles, and this negative potential must travel through the nerve at the rate of nerve-conduction.

Moreover, if two equal nerve impulses traveling in opposite directions meet, they annul one another, for each has exhausted the supply of adsorbed cations, and it takes time for the colloidal particles to attract other cations to their surfaces.

In these simple non-medullated nerves a strong stimulus consumes more of the adsorbed cations than a weak one and thus travels at a proportionately faster rate. Moreover, as it takes time for the colloidal particles to recapture and adsorb new cations, the resting interval for the nerve must be longer for strong than for weak stimuli. Hence, a very strong stimulus can follow a very weak one without any resting interval, for it can still act upon adsorbed cations which the weaker stimulus has not neutralized. The sea water, or the fluids bathing the nerves, are normally alkaline, and thus the OH-ion is in excess. This OH-ion is not adsorbed, but acts as a catalyzer. If we heat the nerve, we would expect its rate to augment from two- to three-fold for every ten degrees, were its activity due solely to the OH-ion; but heat dissociates the adsorbed Na, Ca, and K and thus the resultant rate is reduced, augmenting only in a linear ratio.

This hypothesis does not attempt to explain the nature of the chemical reaction between the adsorbed cations and other elements to form an ion-proteid, but claims that nerve conduction is accompanied by a chemical reaction between the adsorbed sodium, calcium, and potassium cations and some undetermined elements of the protoplasm.

Fuller details of this research will be found in The Proceedings of the National Academy of Sciences (1916, January, Vol. 2, pp. 37-42), and a much more complete paper in the American Journal of Physiology (1916, February, Vol. 39, pp. 375-391).

2. A System for Following Postoperative Patients. DR. FREDERICK W. BANCROFT, New York City.

To appear later in the BULLETIN.

3. Thorium: A New Agent for Pyelography. DR. J. EDWARD BURNS.

To appear later in the BULLETIN.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

FEBRUARY 14, 1916.

1. Medicine in Japan and China. DR. WILLIAM H. WELCH.

To be published later in the BULLETIN.

THE LAENNEC.

FEBRUARY 28, 1916.

1. Tuberculosis in Early Childhood. (Abstract.) DR. ALMA ROTH-HOLTZ.

Dr. Rothholtz made a preliminary report on work done in the Harriet Lane Home on tuberculosis in early childhood and presented the following statistics as the result of her study:

Number of hospital outpatients in Harriet Lane Home....	9,380
Total number of tuberculous patients.....	435
Total number of tuberculous patients under 3 yrs.....	123

AGE.

Under 6 months.....	10 (died, 6)
Under 1 year.....	28 (died, 15)
Under 2 years.....	56 (died, 21)
Under 3 years.....	29 (died, 8)

COLOR.

White	62
Black	61

VON PIRQUET.

Positive	110
Negative	6
Not read	7

EXPOSURE.

Positive	50
Doubtful	13
Negative	39

SYMPTOMS.

Cough	53
Fever	88
Loss of weight	36
Intestinal	22
Convulsions	21

PHYSICAL SIGNS.

Lungs	94
R. U.	34
L. U.	42
R. B.	5
L. B.	11
Râles	65
Effusion	2
Peritoneum	4
Enlarged spleen	48
Tuberculous glands	44
Tuberculous bones	11
Hip	7
Phalanges	7
Spine	7
Ankle	1
Ribs	1
Stenosis	29
Skin	19

X-RAY.

Positive	64
Negative	7
Not done	56

CAUSES OF DEATH.

	Ac. gen. miliary tuberculosis.	Pulmonary tuberculosis.
Under 1 year	13	8
Under 2 years	13	8
Under 3 years	3	2

DISCUSSION.

DR. HAMMAN: Dr. Rothholtz's remarks touch upon some of the vital questions of the anti-tuberculosis campaign. A great deal already has been accomplished in the fight against tuberculosis, but we must admit that our success falls short of what was promised and confidently anticipated. The value of the methods so far used in the campaign was unwittingly exaggerated. From a broad sociological standpoint the treatment of tuberculosis has failed. Home prophylaxis has been no more successful; nurses have shown the futility of this remedy. We have come, as it were, to a halting place, where we must rest and carefully review our work and rearrange plans for the future. It is by no means clear which road we should travel from now on. The growing importance of infection in early childhood has led many to look to this aspect of the question as the one holding the greatest promise for the future.

Not many years ago the transmission and development of tuberculous infection were regarded as settled and simple problems. It was thought that contact with the tuberculous led to infection, and that infection was promptly followed by disease. It was a remarkable insight that led von Behring to break from this general view and place the period of infection in early childhood. Later studies, particularly the observations upon tuberculin hypersensitiveness, have fully confirmed his contention. We now know that nearly all children are infected before they reach the twelfth year.

Another important conclusion that has come from immunological studies upon tuberculosis is the power of infection to protect against reinfection, or perhaps better termed superinfection. The usual form of pulmonary tuberculosis in adults, chronic ulcerative phthisis, is the expression of a high degree of resistance to the disease. How very different are the clinical manifestations of tuberculous disease in adults and the clinical picture Dr. Rothholtz has drawn from her observations upon children.

The difficult problem we face at the present time is to learn how to use this knowledge to practical advantage. On the one hand, if we solicitously guard children against infection an unprotected population will grow up which we are led to infer would rapidly succumb to tuberculosis were it exposed to infection. On the other hand, although we believe that infection successfully overcome is a strong barrier to the development of tuberculous disease, still we have no way of applying this knowledge for prevention. Surely no one would advocate the purposeful exposure of children to infection; and yet to guard them too closely may just as certainly defeat our purpose.

On the basis of what we have learned concerning childhood infection many are inclined to deny all importance to adult infection. In my opinion this extreme is unjustified. While previous infection may protect against occasional and mild reinfection, the barrier breaks down before repeated and massive implantations.

Therefore, to find our way in the anti-tuberculosis campaign we need a better insight into the many details of childhood infection. Such careful studies as Dr. Rothholtz has made will gradually clear our vision.

DR. FORD: The points brought out by Dr. Hamman are particularly interesting. We have not made the impression on tuberculosis that we should have made, and some of us are inclined to believe that one of the reasons is that we have gone on and carried out certain precautions which we all suspected were not effective, such as the disinfection of a house after tuberculosis. -I,

personally, am beginning to think that disinfection carried out by municipal authorities might just as well not be done. You cannot disinfect a house by the methods applied, unless you are willing to devote a very considerable time to it, spend a good deal of money and put an expert in charge of the work. In the majority of cases, disinfection is of doubtful value and is apt to give a false sense of security. That is the opinion of Dr. Dunbar of Hamburg, and has been for a number of years, as the result of his investigations. He has given up gaseous disinfection and substituted for it the washing of the floors and walls up to the height of six feet with soap and water and a strong disinfecting solution. I think he feels that this is an advance. It does not lull the people to sleep, but impresses upon them the necessity of cleanliness. It is also the opinion of Dr. Chapin, one of our best authorities, that many of the measures carried out to control contagious diseases have had little effect upon them and that the time has come when substantial changes should be made in our method of combating them.

DR. PARK: Some of the points brought out by Dr. Rothholz this evening are very striking to anyone who has worked in the Harriet Lane Dispensary. The first and one of the most important is the liability of a young child exposed to tuberculosis to contract the disease. When we find that a mother or father has active tuberculosis, it is probable that the infant has tuberculosis also. When one member of a family of children is infected, usually all the other members of the family are also affected.

Another important point brought out by Dr. Rothholz is that children infected with tuberculosis in their first year do not necessarily die. It is commonly thought that all children infected

with tuberculosis in the first year die, but Dr. Rothholz has found several instances of children infected in their first year who are still living and are to all appearances in good health.

Another interesting observation which she has made is that infants showing papulo-necrotic tuberculides do not necessarily die. It is ordinarily taught that children showing this lesion, which implies that tubercule bacilli have entered the blood stream, die within two or three months.

It is most important to appreciate the clinical differences in the manifestations of tuberculosis in infants and in adults. How often an infant with a disseminated infection appears to be in blooming health, with red cheeks, splendid nutrition and gains steadily in weight! When infants with pulmonary tuberculosis are auscultated, it is very common to find that no râles or definite changes in the breath sounds are present. The earliest and most constant physical sign present in infants with pulmonary tuberculosis is impairment in the percussion resonance, usually over rather large areas.

It is interesting to note that Dr. Rothholz's statistics show enlargement of the spleen to be present in 50 per cent of the cases. Enlargement of the spleen in very young infants means usually either syphilis or tuberculosis.

2. Carcinoma of Pleura. DR. STANHOPE BAYNE-JONES.

To appear later in the BULLETIN.

3. Choroidal Tubercles in General Miliary Tuberculosis. DR. R. L. RANDOLPH and DR. H. C. SCHMEISSER.

BOOKS RECEIVED.

Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

1. *Manual of Surgery.* By Alexis Thomson, F.R.C.S. Ed., and Alexander Miles, F.R.C.S. Ed. Volume first. General Surgery. Fifth edition, revised and enlarged, with 289 illustrations. 1915. 12°. 801 pages.

2. *Manual of Surgery.* By Alexis Thomson, F.R.C.S. Ed., and Alexander Miles, F.R.C.S. Ed. Volume second. Regional Surgery. Fifth edition, revised and enlarged with 301 illustrations. 1915. 12°. 948 pages.

3. *Practical Prescribing and Treatment in the Diseases of Infants and Children.* By D. M. Macdonald, M.D., F.R.C.P.E. 1915. 16°. 199 pages.

4. *Cerebro-Spinal Fever.* By Thomas J. Horder, M.D. With seventeen illustrations. 1915. 16°. 179 pages.

Oxford War Primers. Henry Frowde, London; Hodder & Stoughton, London.

1. *Gunshot Injuries of Bones.* By Ernest W. Hey Groves, M.D., M.S. (Lond.), F.R.C.S. (Eng.). 1915. 16°. 128 pages.

2. *Nerve Injuries and Shock.* By Wilfred Harris, M.D. (Cantab.), F.R.C.P. (Lond.). 1915. 16°. 127 pages.

3. *Injuries of Joints.* By Robert Jones, Ch. M., F.R.C.S. (E. & L.). 1915. 16°. 189 pages.

4. *Abdominal Injuries.* By Rutherford Morison and W. G. Richardson, M.B., F.R.C.S. 1915. 16°. 116 pages.

5. *Wounds of the Thorax in War.* By J. Keogh Murphy, M.C. (Cantab.), F.R.C.S. 1915. 16°. 156 pages.

6. *Wounds in War; Their Treatment and Results.* By D'Arcy Power, M.B. Oxon., F.R.C.S. (Eng.). 1915. 16°. 108 pages.

7. *Surgery of the Head.* By L. Bathe Rawling, M.B., B.C. (Cantab.), F.R.C.S. (Eng.). 1915. 16°. 150 pages.

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BULLETIN

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CHEMICAL STUDIES ON A CASE OF BICHLORIDE POISONING.

By D. SCLATER LEWIS, M. D., and T. M. RIVERS, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital, Baltimore.)

Owing to the frequency of poisoning by mercuric chloride, the clinical picture is well known, and numerous articles are to be found dealing with this aspect of the condition.¹

The pathological features have also received a considerable amount of attention. The best description of the characteristic sublimate kidney is to be found in Heineke's recent article.²

The excellent work of Lieb and Goodwin,³ and of Lambert and Patterson⁴ has done much to place the treatment of the condition on a more substantial foundation. Thanks to their suggestions, we now are able to save a considerable number of cases that almost certainly would have terminated fatally with the old methods of treatment. They have emphasized the value of prolonged and energetic measures directed to the removal of mercury from the body by every means at our disposal. Frequent lavage of the stomach and irrigation of the colon afford the most efficient means of elimination, and should

be carried on till mercury can no longer be demonstrated in the washings.⁵

The key-note of the present mode of treatment is *elimination*.

Studies on the metabolism in bichloride poisoning, however, have been of a very superficial character, in most cases confined to a few observations on the level of the non protein nitrogen of the blood toward the end of longer or shorter periods of anuria. Our chemical studies have been more extensive than any reported in the past, and will, therefore, be given in some detail.

HISTORY.

Med. No. 34753. Mrs. E. D., Age 20; Married. Admitted to The Johns Hopkins Hospital, Sept. 21, 1915. Discharged Oct. 19, 1915.

Complaint.—Bichloride poisoning.

F. H.—Not important.

P. H.—Bichloride douches have been taken for some time, on account of leucorrhœa.

¹ Foster, N. B.: Arch. Int. Med., 1915, XV, 755.

Meyerstein: Münch. med. Wehnschr., 1911, LVIII, 1965.

² Heineke: Ziegler's Beiträge, 1909, XLV, 197.

³ Lieb and Goodwin: Jour. Am. Med. Assn., 1915, LXIV, 2041.

⁴ Lambert, S. W., and Patterson, H. S.: Arch. Int. Med., 1915, XVI, 865.

⁵ A very sensitive test for mercury in the excreta is described by Vogel (Karl) and Lee (Ivan): Jour. Am. Med. Assn., 1914, LXII, 531.

P. I.—Twenty-four hours before admission the patient took, on an empty stomach, what she thought to be a headache tablet. In half an hour vomiting commenced and persisted till her admission. At first the vomitus was blue; later, colorless. It never contained blood. A physician saw her ten hours after the accident, but did not prescribe. There were several watery stools during the night, but no melena; no abdominal pain. There were severe cramps in the legs. She voided during the morning of the 21st before admission. She walked to the hospital, and on arrival complained of being very nauseated, and of having a metallic taste in her mouth.

P. E.—T. 100°. P. 96. R. 24. (9 a. m.) Well nourished; drowsy; no edema; no evidence of corrosion about the mouth and throat. Tongue heavily coated; breath foul. Lungs clear. Heart not enlarged; soft systolic murmur at apex. Pulse regular. B. P. (Tycos) 105/85. Abdomen scaphoid; moderate epigastric tenderness; liver and spleen not felt. Reflexes normal. Blood: Wassermann negative. Hgb. 95% (Sahli). R. B. C. 5,760,000. W. B. C. 10,880. No urine could be obtained for examination.

Course in Hospital. Vomiting was persistent during the first 14 days, on three occasions amounting to more than 800 cc. in the 24 hours. Between the third and tenth days, the vomitus contained many blood clots. Diarrhea was not a troublesome feature, but melena was present for 21 days. Stomatitis was never severe. It appeared on the sixth day, persisted till the twelfth day, and was localized about the openings of the salivary ducts. Anuria began 18 hours after the accident and lasted six days. The patient was catheterized twice during the period, but only a few cubic centimeters of thick slimy fluid were obtained. This did not contain tube casts or any measurable amount of urea, and was not thought to be urine. On the eighth day of the disease, the anuria ceased and the urinary output gradually rose to a high level which was maintained for some time by a forced intake of water. During the anuric period, the patient became more and more drowsy, but this lethargy disappeared soon after the reestablishment of urinary secretion.

The highest temperature was 100.2° F. The pulse was extremely variable on the seventh, eighth and ninth days, but was never above 110. The blood pressure varied from 110/85 to 130/98 (Tycos). Repeated examination of the lungs and abdomen failed to show anything of interest. There was no recognizable edema at any time.

The patient was discharged "well" on the twenty-seventh day. She has been seen a number of times since, and is apparently in perfect health.

TREATMENT.

The treatment may be summarized as follows:

1. Gastric lavage twice or thrice daily for four days.
2. Rectal saline injections—250 cc. physiological salt solution, with 12 gm. sodium bicarbonate every three hours for three days. For the next 12 days, normal salt solution was given by proctodysis, in amounts averaging 1050 cc. daily. On one of these days, the drip was omitted entirely because of incomplete absorption.

3. On the eighth day, 300 cc. of a 5 per cent solution of glucose were given intravenously, in part for its diuretic effect, in part for the protein-sparing action of the carbohydrate. On the ninth, tenth and eleventh days, respectively, 500 cc. of a 10 per cent solution were given.

4. Water was forced by mouth from the onset. It was vomited at first but was retained in large part after the twelfth day.

5. Sweat baths were given twice daily for 14 days, and were always followed by satisfactory reactions.

6. Diet: Milk was given after the fourth day, a meat-free diet on the seventeenth day, and full diet was allowed after the twenty-sixth day.

LABORATORY FINDINGS.

The chemical studies were of particular interest. The patient was perfectly conscious during her entire illness, and able to cooperate to the fullest extent. The cooperation of the nursing staff was excellent, and we have every reason to believe that the specimens obtained were complete.

The facts presented fall under three main heads:

A. Chemical Studies of the Blood.

B. Chemical Studies of the Urine.

C. Observations on the Acid-Base Equilibrium of the Body.

A. CHEMICAL STUDIES OF THE BLOOD.

The total non-protein nitrogen* and urea nitrogen† of the blood, and the sodium chloride‡ content of the plasma, were determined at frequent intervals. These values appear in Table I. The blood sugar§ was estimated on two occasions.

TABLE I.—ANALYSES OF BLOOD.

Date.	Day of disease.	T. N. P. N. mg. per 100 cc.	Urea nitrogen, mg. per 100 cc.	Percentage of T. N. P. N. pre- served in urine.	Sodium chloride of plasma, mg. per 100 cc.	Sodium chloride of whole blood, mg. per 100 cc.	Blood sugar, mg. per 100 cc.	Amplified coeffi- cient of urea excretion.	Phenol output in 24 hours.
Sept.									
22	3	81	55	67.8	x
24	5	147	100	68.0	455	x
27	8	184	133	72.3	410
28	9	173	142	82.0	402	199
29	10	178	148	83.2	385	362	1.09
30	11	170	141	83.0	390	379	1.36	±
Oct.									
2	13	125	102	81.6	463	455	0.55 ¹⁰⁰	11.5%
4	15	78	55	70.5	530	521	0.408 ¹⁰⁰	27.5%
6	17	42	23	54.8	587	572	147	0.186 ¹⁰⁰	35.0%
8	19	26	11	42.4	587	568	0.124 ¹⁰⁰
13	24	22	8	36.4	595	569	0.06	45.0%
18	29	22	11	50.0	0.11

* Day of disease on which test was done.

1. *The Total Non-protein Nitrogen and Urea Nitrogen.*—Foster,¹ Phillip,¹¹ Woods,¹² and Myers and Lough¹³ have published isolated observations on the non-protein nitrogen in bichloride poisoning. Their results were usually obtained

* For the T. N. P. N., a modification of Folin's micro-method was employed. Following Dr. B. B. Turner's suggestion, the NH₃ was driven from the digestion mixture by a combination of heat and aeration, the absorption tube being cooled in a water trough.

¹ Marshall's Urease Method. Jour. Biol. Chem., 1913, XV, 487.

¹¹ Modified Volhard-Charpentier Method. Ambard and Weill: Sem. méd., Mai 8, 1912.

¹² Benedict and Lewis: Jour. Biol. Chem., 1915, XX, 61.

¹³ Foster, N.: Loc. cit.

¹⁴ Phillip: Med. Klin., 1913, IX, 912.

¹⁵ Woods: Arch. Int. Med., 1915, XVI, 577.

¹⁶ Myers and Lough: Arch. Int. Med., 1915, XVI, 536.

shortly before the exitus of the patient, and are from 20 to 30 percent higher than ours. Underhill¹⁴ has reported a series of determinations of the blood urea in four cases. In one of these, recovery took place after the urea nitrogen had been over 150 mg. per 100 cc. for 18 days, and on two occasions above 240 mg.

In our case the T. N.-P. N. reached a maximum of 184 mg. per 100 cc. on the eighth day. It remained stationary for four days and then rapidly fell to normal. The curve of the urea nitrogen was of the same type. It reached its maximum of 148 mg. on the 10th day and then returned to normal.

2. *Factors Influencing the Rate of Accumulation of Waste Nitrogen in the Blood.*—Marshall and Davis¹⁵ have shown that urea is distributed uniformly throughout the tissues of the body with the exception of the bone, fat and kidneys. They have calculated that every gram of urea retained by an individual of 70 kg. will cause a rise of 1.33 mg. of urea per 100 cc. of blood. It is permissible to apply these figures to the urea nitrogen of the blood and to assume that every gram of nitrogen retained as urea will give a rise of 1.33 mg. of urea nitrogen per 100 cc. of blood.

Frequent observations of fasting individuals have shown that the usual excretion of nitrogen in the urine, during the first week, is in the neighborhood of 12-13 gm. *per diem*.¹⁶ Approximately, 85-90 per cent of this nitrogen (*ca.* 11 gm.) is excreted as urea. Our patient weighed 68 kg. on admission and she was starved, as practically no food was retained during the first week of her illness. We are, therefore, justified in assuming that, being anuric, she would retain approximately 11 gm. of urea nitrogen per day, as a result of the tissue destruction which occurs in a normal individual during starvation. This would correspond to a daily rise of about 14 mg. of urea nitrogen per 100 cc. of blood during the first week. The actual daily rise of the blood urea nitrogen between the third and fifth days was 22.5 mg., *i. e.*, 7.5 mg. above the amount calculated to result from simple starvation. This excess must have been due, in large part, to an increased tissue destruction caused by the toxic action of the bichloride.

From the fifth to the eighth days, the rise was only 11 mg. per day—a little lower than the estimated value. The small amount of nitrogen excreted in the urine of the eighth day was quite insufficient to account for the diminished rate of accumulation. It is interesting to note that on two of these days the patient received glucose infusions (80 gm. of sugar in all), and this drop in the rate of accumulation may possibly be due to the protein-sparing action of the carbohydrate.

On the two following days, there was a further drop in the rate of accumulation to 9 and 6 mg. of urea nitrogen per 100 cc. The nitrogen output on these days averaged 3.5 gm. These outputs would have decreased the calculated rise in the blood urea nitrogen to 11 mg. per day. On these days, further

glucose infusions were given, and the discrepancy may again be referred to the protein-sparing activities of the carbohydrate.

Austin and Leopold¹⁷ have shown experimentally that the administration of glucose has a distinct protein-sparing action in the acute renal insufficiency following bilateral ligation of the ureters. They have also found that animals receiving glucose have survived the operation longer than those that did not receive it.

At no time, in spite of the long period of anuria, did the blood nitrogen reach the high values reported by other observers, and we are justified in assuming that the glucose was responsible, to a certain degree, for the lower rate of nitrogen accumulation. Mercuric chloride causes an acute toxic necrosis of the renal epithelium, which is followed by complete regeneration if the patient survives the initial period of renal insufficiency. Any procedure, therefore, which tends to reduce tissue destruction and keep the blood nitrogen at a lower level will also tend to prolong the life of the individual and so increase the chances of recovery. The intravenous infusion of glucose in these patients who cannot tolerate carbohydrate by mouth is a means to this end.

3. *Sodium Chloride in the Plasma.*—When one considers the frequency of anuria in bichloride poisoning, and the apparent chloride retention so often seen after the urinary flow is reestablished, one is struck with the rarity of outspoken edema in these individuals. V. Monakow¹⁸ has reported one case with definite edema, but this is unusual. The data presented with his case show that there was no relation between the degree of salt retention and the weight of the patient,¹⁹ and that there was no sweeping out of retained salt, even after the complete restoration of renal function. It is evident from the above that we are not dealing with the type of retention usually present in "chloruremic" nephritis.

Working with rabbits, Heineke and Meyerstein²⁰ found a marked depression of the plasma chlorides in chromium nephrosis. Values of 360 to 400 mg. per 100 cc. were not at all uncommon, whereas the normal range was between 550 and 610 mg. Animals with these low salt concentrations showed little, if any, edema. If large quantities of salt were administered (1.0-1.5 gm. per kg. per day), the concentration of chlorides in the serum rose rapidly to high values—750 to 790 mg.—and the animals then became very edematous.

Woods²¹ has also found an extremely low concentration of sodium chloride in the blood from a case of bichloride poisoning on the fifth day of anuria.

The plasma chlorides have been determined at frequent intervals in the present instance. On the fifth day, the amount

¹⁷ Austin, J. H., and Leopold, S. S.: *Proc. Soc. Exp. Biol. & Med.*, 1915, XIII, 3.

¹⁸ V. Monakow: *Deutsch. Arch. f. klin. Med.*, 1914, CXV, 224.

¹⁹ Javal: *Presse méd.*, Avr. 6, 1914, 477.

²⁰ Kovesi and Roth Schultz: *Pathologie u. Therapie der Niereninsuffizienz*, 1904, 157. (Quoted by Ambard, *Physiologie norm. et path. des reins*, Paris, 1914).

²¹ Heineke and Meyerstein: *Deutsch. Archiv. f. klin. Med.*, 1907, XC, 101.

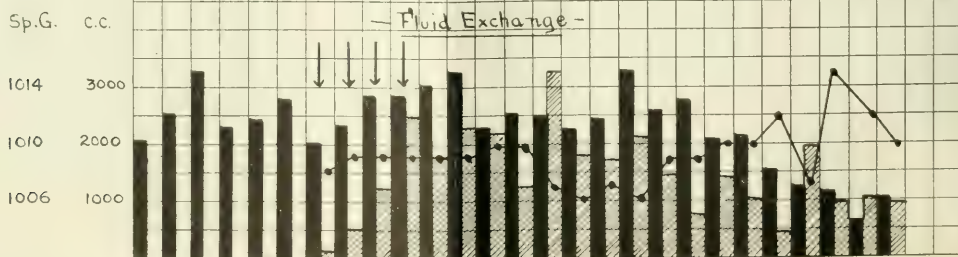
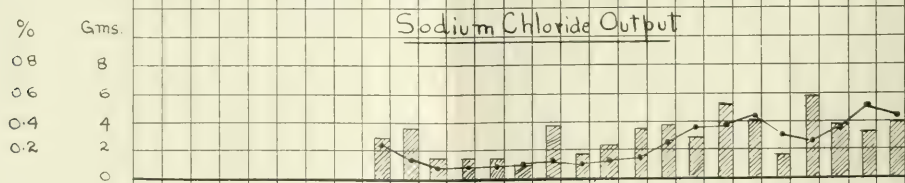
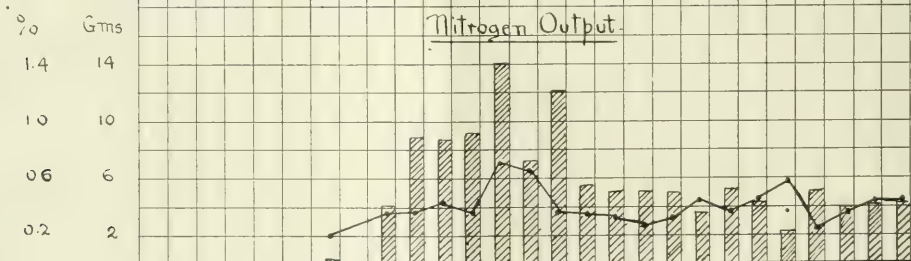
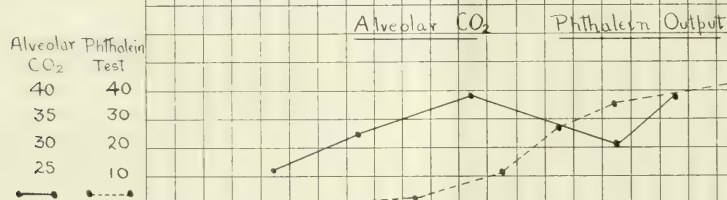
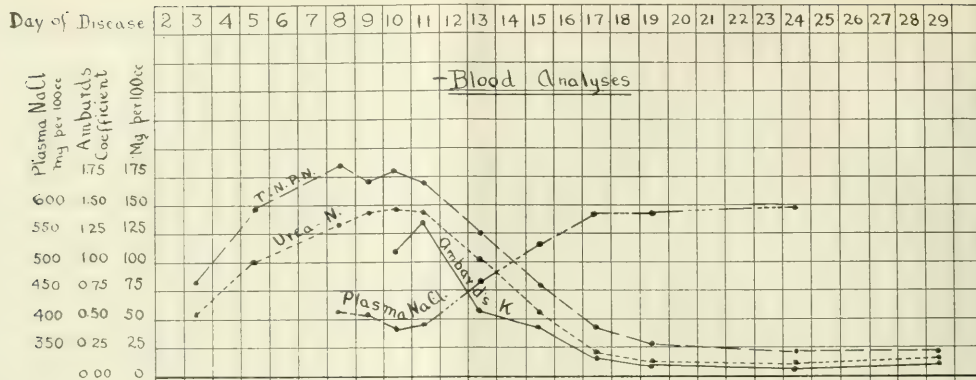
²² Woods: *Arch. Int. Med.*, 1915, XVI, 577.

¹⁴ Underhill, A. J.: *N. Y. Med. Jour.*, 1915, CII, 662.

¹⁵ Marshall and Davis: *Jour. Biol. Chem.*, 1914, XVIII, 53.

¹⁶ Munk: *Arch. f. Path. Anat.*, 1893, CXXXI, (Suppl.) 25.

¹⁷ Johansson, Landergrén, Sonden and Tigerstedt: *Skandin. Arch. f. Physiol.*, 1896, VII, 54.



Glucose Infusions →

present was 455 mg. per 100 cc. (normal values, 580-620 mg.). On the eighth and ninth days there was a progressive decrease, and on the tenth day, the plasma chlorides reached their minimum value of 385 mg. per 100 cc. From this time, the quantity gradually increased, but only reached a normal level on the seventeenth day.

Ambard and Weill²² showed that the urine contained practically no salt if the concentration in the blood were below a certain amount. They called this critical concentration the *threshold of excretion*. Its normal value was found to be in the neighborhood of 562 mg. per 100 cc. of plasma.

The low output of chlorides during the first 2½ weeks of the disease can be explained quite readily by the depression of the sodium chloride of the blood below the "threshold." Reference to the chart and tables will show that the salt outputs were very low until the plasma chlorides had risen above the threshold of excretion. The retention of chlorides in mercuric chloride poisoning is, therefore, of the same general type as that seen in pneumonia.²³ These observations do not explain the mechanism of the removal of sodium chloride from the blood, but they do show that the apparent retention is not due to any impermeability of the kidney to salt.

There are three possible explanations of the low concentrations of the plasma chlorides:

1. The sodium chloride may have been excreted by the alimentary tract and by the skin. A point in favor of this hypothesis is that the amount of sodium chloride decreased regularly during the period of severe vomiting, and the first tendency to rise was shown on the thirteenth day, 24 hours after the vomiting had ceased. The absence of any sweeping out of "retained salt" after recovery, both in this case and in that reported by v. Monakow,²⁴ would seem to favor the theory of complete removal of salt from the body, rather than any retention in the tissues.

2. The fall of the blood chlorides may have been due to a marked hydemie plethora with a consequent dilution of the constituents of the blood. Georgopoulos²⁵ has suggested this as being the probable explanation of the low concentration of chlorides in the serum of rabbits with a chromium nephrosis. The studies of the rate of rise of the blood urea, and the absence of any very marked change in the blood-count,²⁶ make this supposition an unlikely one.

3. The tissues may have developed an increased affinity for salt and have withdrawn it from the blood. Such a condition would presuppose the presence of a "dry chloride" retention, as there was no recognizable edema at any time during the patient's stay in the hospital. Had such a dry retention actually been present, there should have been a sweeping-out of salt when normal renal function was reestablished. No such increased elimination of chlorides could be demonstrated.

²² Ambard and Weill: *Sem. méd.*, Mai 8, 1912.

²³ McLean, F. C.: *Jour. Exper. Med.*, 1915, XXII, 366.

Peabody, F. W.: *Jour. Exper. Med.*, 1913, XVII, 71.

²⁴ *Loc. cit.*

²⁵ Georgopoulos: *Ztschr. f. klin. Med.*, 1906, LX, 411.

²⁶ First day: R. B. C. 5,760,000. Hgb. (Sahli) 95%. 17th day: R. B. C. 4,176,000. Hgb. (Sahli) 82%.

In the present case, no one explanation can be regarded as being of an entirely satisfactory nature. One can say, however, that there is no salt retention of a type which would contraindicate the use of normal salt solution as a means of forcing fluid on the patient. It is even possible that the body may require salt to make up for the chloride deficit, and that the use of moderate amounts of salt may be a beneficial, rather than a harmful procedure.

4. *The Blood Sugar*.—Frank²⁷ refers to the frequency of a glycosuria of moderate degree in the experimental nephroses caused by the heavy metals. This glycosuria is caused by a depression of the glucose threshold of the kidney, and, as a rule, no hyperglycemia is associated with it. This lowering of the glucose threshold is interesting in relation to the lowering of the threshold for salt which is also present in this type of renal injury.

We have determined the blood sugar on two occasions, the value of more systematic observations being vitiated by the frequent intravenous infusions of glucose. On each occasion there was a definite hyperglycemia (199 and 147 mg. per 100 cc.), which could be referred to the therapeutic procedures in use at the time.

5. *Ambard's Coefficient of Urea Excretion*.²⁸—The return of renal function to normal has also been followed by means of Ambard's coefficient of urea excretion. This coefficient is a constant relation which exists between the concentration of urea in the blood and the rate of excretion of urea in the urine. The normal range of the coefficient is from 0.07 to 0.09. With decreasing renal function, the coefficient shows a tendency to rise, and with increasing function, a tendency to fall.

It is calculated by means of the following formula:

$$K = \frac{Ur}{D \times \frac{70}{P} \times \frac{1}{25}}$$

where K = Coefficient of urea excretion;

Ur = Urea in grams per liter of blood;

D = Output of urea in grams per 24 hours;

C = Concentration of urea in grams per liter of urine;

P = Weight of patient in kg.

The rate of output, D , is corrected for a standard concentration of 25 gm. of urea per liter of urine, and for a standard weight of 70 kg.

In chronic nephritis, coefficients above 0.4 are seen only in the late stages of the disease when there is such outspoken renal insufficiency that death may be expected within a relatively short time. High coefficients may also be obtained in acute nephritis, and in the nephroses, but here they do not have the same significance as in the former cases. In the acute cases, the impairment of renal function may subside and, with improving function, the constant will fall to a more normal figure.

²⁷ Frank: *Arch. f. exper. Pathol. u. Pharmacol.*, 1913, LXXII, 387.

²⁸ Ambard, L.: *Compt. rend. Soc. de biol.*, 1910, pp. 411, 506. *Physiol. norm. et pathol. des reins*, Paris, 1914.

In the present instance, the coefficient was infinity during the days of anuria. There was no excretion of urea and the fraction

$$\frac{U_r}{D \times \frac{70}{P} \times \frac{1}{\sqrt{25}}} \text{ became } \frac{U_r}{0} = \infty$$

On the tenth day of the disease, the coefficient fell to 1.09. On the eleventh day, in spite of a fall in the blood urea from 1.8 to 1.11 mg., there was a slight rise in the coefficient to 1.36. On the following days there was a rapid fall in the constant (0.55, 0.408, 0.186, 0.124, etc.), till a normal level was reached on the twenty-fourth day. During the early stages of recovery there was a close agreement between the variations in the coefficient and in the blood urea. Later, the coefficient's rate of fall became much slower than that of the urea in the blood, and the former did not reach a normal level until a week after the blood urea had been within normal limits.

In the chronic nephropathies, with no marked change in the functional capacity of the kidney from day to day, Ambard²² and McLean²³ have found that the coefficient is remarkably independent of the concentration of the urea in the blood. With occasional exceptions, the same independence has been noted in a series of observations to be published by one of us in the near future. For every change in the level of the blood urea (U_r), there is a corresponding change in the rate of out-

put (D), with the result that $\frac{U_r}{\sqrt{D}}$, etc., remains constant.

Therefore, had the injury to the kidney in this case been a permanent one, the coefficient would have remained at the original level (1.09), despite the changing concentration of urea in the blood. The damage, however, was of a transient nature, and, with the return of the renal epithelium to a normal functional state, the kidney was able to respond more and more fully to the stimulus afforded by the blood urea. As

a result, the numerator of the fraction $\frac{U_r}{\sqrt{D}}$, etc., decreased at a

greater rate than the denominator, and there was a corresponding drop in the value of K until it eventually reached the normal level.

6. *The Phthalein Test.*—The phthalein test was done according to Rowntree and Geraghty's original technique.²⁴

On the ninth day, no recognizable amount of the dye was excreted. Two days later, an unreadable trace was present in the two-hour specimen. Subsequent tests showed a continuous increase in the rate of excretion, and there was a low normal output (45 per cent on the twenty-fourth day) one week after the blood urea and total non-protein nitrogen had shown an apparently normal renal function.

²² Ambard: *Physiologie normale et pathologique des reins*, Paris, 1914.

²³ McLean, F. C.: *Jour. Exp. Med.*, 1915, XXII, 212; 366.

²⁴ Rowntree, L. G., and Geraghty, J. T.: *Arch. Int. Med.*, 1912, IX, 284.

In experimental nephritis it has been shown²⁵ that the phthalein output drops to its minimum rate of excretion some time before the retention of nitrogen has reached its maximum; that, with a return to normal function, the phthalein reaches its normal rate of excretion before all of the retained nitrogen has been eliminated. The reversal of the order of return to normal in the present instance is probably due, in part, to the low protein intake, and in part to the assimilation of considerable amounts of nitrogen in the repair of tissues broken down during the initial period of starvation and intoxication. As a result, there was relatively little nitrogen to be excreted, and this could be eliminated by the kidney, even though its function was definitely impaired. Retention of waste nitrogen occurs only when the end-products of metabolism accumulate at a greater rate than they can be eliminated by the kidney.

TABLE II.—ANALYSES OF THE URINE.

Date.	Day of disease.	24-hour volume cc.	Sp. G.	Reaction.	Albumin, gm. per litre.	Total nitrogen.	Sodium chloride.	Glucose.	Casts.	Epithelial cells.	W. B. C.	R. B. C.
Sept. 21-26	2-7			Anuric.								
27	8	110 1008		Alkaline	3.3	0.23	0.25	+++	+	0
28	9	145 1099		"	4.5	+++	+	0
29	10	1185 1099		"	3.5	0.335	3.950	0.242	0.41	+++	+	Few.
30	11	2510 1099		Acid	++	0.356	8.950	0.14	3.51 T.	+++	+	Few.
Oct. 1	12	1770 1099		"	++	0.468	8.28	0.08	1.42	0	+	0
2	13	2241 1099		"	0.338	0.7	0.08	1.79	0	+	+	0
3	14	2095 1010		"	0.73	0.676	14.160	0.08	1.60 T.	+	+	0
4	15	1221 1099		"	T.	0.612	7.5	0.08	0.80	0	+	0
5	16	3260 1007		Alkaline	0.5	0.572	12.130	0.12	3.91 T.	+	+	0
6	17	1720 998		Acid	0.5	0.308	5.360	0.08	1.42	0	+	0
7	18	1670 1007		"	T.	0.289	4.960	0.14	2.34 T.	0	0	0
8	19	220 1006		"	F.T.	0.239	5.070	0.16	3.39	0	0	0
9	20	1440 1009		"	T.	0.302	5.210	0.26	3.74	0	+	0
10	21	78 1009		"	T.	0.472	5.310	0.38	2.66	0	+	0
11	22	1365 1010		"	+	0.868	5.550	0.38	3.39	0	+	0
12	23	562 1010		"	0.25	0.47	4.520	0.12	4.04	0	+	0
13	24	430 1012		"	T.	0.58	2.390	0.34	1.46	0	+	0
14	25	1940 1007		"	0	0.26	5.060	0.28	5.43	0	+	0
15	26	1065 1015		"	0	0.39	3.460	0.38	0.82	0	0	0
16	27	1629 1012		"	0	0.43	4.380	0.50	5.10	0	0	0
17	28	930 1010		"	0	0.49	1.560	0.42	3.91	0	0	0
18	29			Discharged.								

* (C. T. M.)

If the protein intake be sufficiently reduced, and if large quantities of carbohydrate be added to the diet, the amount of nitrogen to be excreted may be so reduced that the damaged kidney can excrete it completely and there will be no accumulation in the blood. Under such conditions, the actual state of renal function will not be shown by a simple estimation of the non-protein nitrogen of the blood. It will be more accurately indicated by a comparison of the concentration of this substance in the blood with its rate of excretion in the urine. This can be done most satisfactorily by the determination of Ambard's coefficient of urea excretion, which is absolutely independent of the nitrogen intake of the individual. In reality, the phthalein test is also based on the same fundamental principles. A known amount of the dye is injected and its rate of excretion determined. The test is, therefore, a comparison between the rate of excretion of the dye and the concentration of the dye in the body.

²⁵ Fitz, K.: *Arch. Int. Med.*, 1915, XV, 524.

The results in the present instance are in strict accord with the above, and we may assume that the slower return to normal of the phthalein excretion and the coefficient are more accurate indications of the establishment of a normal renal function than the more rapid drop of the blood urea and T. N.-P. N.

B. STUDIES OF THE URINE.

1. *Fluid Exchange*.—The average fluid intake during the initial period of anuria was 2500 cc. daily. We were not able to make any exact records of the output in sweat, stools or vomitus during this period. From a study of the fluid exchange during the subsequent period of elimination, and from the absence of edema, we are justified in assuming that a considerable portion of the fluid taken during the first week was eliminated by the gastro-intestinal tract and by the skin.

Between the eleventh and twentieth days, there was a consistent polyuria; this was caused more by the high fluid intake than by any marked retention of fluid during the week of anuria. During the third week the urinary output reached more normal values, corresponding with the gradual diminution of the amount of fluid taken by the patient.

2. *Specific Gravity*.—The specific gravity curve is of considerable interest. It showed a marked degree of fixation in the early stages of returning renal function, the maximum range being from 1008 to 1010. This might not have been of any particular importance had the daily output of urine also remained constant, but during this period there were great changes in the daily volumes of urine passed (287 to 2500 cc.), without any corresponding variation in the specific gravity.

Mosenthal³³ has shown that considerable information regarding the condition of renal function may be derived from a study of the specific gravity of the urine. He has found that, in nephritis, marked fixation, at a low level, occurs only in the severest types. This fixation is characteristic of the kidney which has absolutely no reserve power, and which is compelled to function constantly at its maximum capacity in order to eliminate the end products of metabolism.

A reference to the curve of blood urea and total non-protein nitrogen will show that it was only after these values had fallen to normal that any variation occurred in the specific gravity. At first there was a drop in the specific gravity, showing that the amounts of waste material to be excreted had fallen below the level necessary to stimulate the kidney to its maximal concentrating power. During the second and third weeks, the specific gravity showed greater variations from day to day, and this was coincident with the improvement in renal function. Towards the end of the period of observation, the kidneys began to show relatively normal concentrating power, considering the fact that the patient's diet was poor in protein and rich in carbohydrate.

3. *Albumin*.—On the first three days after the cessation of anuria, albumin was present in considerable amounts. As the volume of urine increased, the amounts fell rapidly, and no albumin was found in the urine after the twenty-fourth day.

4. *Sodium Chloride*.³⁴—The output of salt was extremely small during the first week of urinary excretion. We have already discussed the underlying causes of this apparent retention and have found it to be due to the marked lowering of the concentration of the plasma chlorides. With the return of normal concentrations of sodium chloride in the blood, the usual output of chlorides in the urine was reestablished. There was no sweeping out of chlorides after the recovery of normal function.

5. *Nitrogen*.—The total nitrogen excreted in the urine was determined by the Kjeldahl process, after the removal of the albumin by means of heat and acetic acid. There was an initial period of increasing excretion, followed by a few days of maximal renal activity during which the retained nitrogen was eliminated, and, finally, a period of approximate nitrogen equilibrium.

The functional power of any tissue may be gauged by its ability to respond to stimulation. The non-protein nitrogen of the blood may be regarded as the stimulus applied to the kidney, and the quantity of nitrogen excreted as the response of the kidney to that stimulus. It is also evident that the response to a given stimulus will be greater or less, according to the functional capacity of the renal epithelium. A comparison of the non-protein nitrogen of the blood from the eleventh to the seventeenth days with the nitrogen output during the same period is of considerable interest. During these eight days, the non-protein nitrogen fell from 170 mg. to 42 mg. per 100 cc., but the rate of output of nitrogen did not show any downward change at all comparable with the marked fall in the nitrogen of the blood. This is a direct evidence of the improvement of renal functions as, with a constantly decreasing stimulus, the renal epithelium was able to excrete amounts of nitrogen as great or greater than had been possible in the earlier periods with much higher grades of stimulation.

C. OBSERVATIONS ON THE ACID-BASE EQUILIBRIUM.

Although the presence of acidosis in uremia was recognized over 25 years ago by von Jaksch,³⁵ but little has been added to our knowledge of the subject until very recently.

In 1912, Straub and Schlayer³⁶ determined the CO₂ tension of the alveolar air in a series of cases of uremia, and found a fairly uniform decrease in the carbon-dioxide tension. They concluded that a definite acidosis was present in every case of uremia and that the uremic picture was due in large part to this acidosis. From the results of an exhaustive study of the blood and urine, Sellards³⁷ decided that an acidosis was present in many of the severer cases both of acute and chronic nephritis, as well as in outspoken instances of uremia. Palmer and Henderson³⁸ also reached the same conclusions from studies of the acidity of the urine, and the rate of excretion

³⁴ Sodium chloride was estimated by the Volhard method.

³⁵ Von Jaksch: *Ztschr. f. klin. Med.*, 1889, XIII, 350.

³⁶ Straub and Schlayer: *Münch. med. Wchschr.*, 1912, LIX, 569.

³⁷ Sellards, A. W.: *Bull. J. H. H.*, 1914, XXV, 141.

³⁸ Palmer, W. W., and Henderson, L. J.: *Arch. Int. Med.*, 1915, XVI, 109.

³³ Mosenthal, H. O.: *Arch. Int. Med.*, 1915, XVI, 733.

of ammonia in nephritis. They found a marked decrease, both in the percentage of total nitrogen excreted as ammonia and in the absolute amount of ammonia excreted in the severer cases. The low excretion of ammonia was considered a protective mechanism. The damaged kidney could not excrete the acid radicals, and consequently ammonia was retained by the body to neutralize them. In their opinion, the acidosis of nephritis was due wholly to the retention of acid, and not, as is the case in diabetes mellitus, to the overproduction of acid bodies. Howland and Marriott²⁵ are of the same opinion. Peabody²⁶ has repeated Straub and Schlayer's work, and has found that the CO₂ tension of the alveolar air gives evidence of a severe grade of acidosis in many cases of uremia. He has shown that the acidosis has no part in the causation of uremia, but is merely an attendant symptom. He has found it possible to control the acidosis with infusions of sodium bicarbonate, but, while the air hunger may disappear, there seemed to be no tendency for the coma or the uremic symptoms to be changed in any way.

In the present instance, the examinations of the acid-base equilibrium were decidedly interesting, although apparently contradictory in nature. The carbon-dioxide tension of the alveolar air was distinctly low during the period of anuria, being 26.8 mm. of Hg. on the sixth day. Three days later (two days after the cessation of anuria) it had risen 33 mm., and on the thirteenth day had reached a normal value of 39 mm. Five days later, the CO₂ tension dropped to 30.6 mm., but again rose to normal 48 hours later.

The low CO₂ tension on the sixth and ninth days gives evidence of a marked acidosis at that time. This finding is in accord with the ideas of Palmer and Henderson that the acidosis of nephritis is due to an imperfect excretion of the acid radicals, as, at the time of severest acidosis, there was anuria with complete retention of the end-products of metabolism usually excreted in the urine.

Studies of the ammonia excretion on the seventh and ninth days also seem to agree closely with Palmer and Henderson's findings, the amounts excreted being small, both in absolute amount and also in relation to the total nitrogen of the urine.

Sellards, on the other hand, has shown that, in the absence of a cystitis, an alkaline urine is never excreted during acidosis. Yet, coincidentally with the above findings, which would seem to indicate the presence of a outspoken acidosis, the urine of the seventh, eighth and ninth days had a definitely alkaline reaction. On the eleventh and twelfth days, the urine was distinctly acid and the output of ammonia dropped still further, so that only 1.5 per cent and 2 per cent of the total nitrogen was excreted as ammonia. This should have indicated an increasing degree of acidosis, but in spite of this, the carbon-dioxide tension of the alveolar air rose to normal, showing a disappearance of the acidosis, as measured by this means.

²⁵ Howland, J., and Marriott, W. McK.: *Bull. J. H. H.*, 1916, XXVII, 63.

²⁶ Peabody, F. W.: *Arch. Int. Med.*, 1914, XIV, 236; 1915, XVI, 955.

Studies of the hydrogen-ion concentration of the blood²⁷ did not reveal a definite acidosis at any time during the patient's stay in the hospital.

In the interpretation of our findings the main difficulty lies in correlating the depressed alveolar CO₂ tension and the low ammonia coefficient with the excretion of an alkaline urine. Reference to the literature²⁸ shows that urine excreted during the early stages of mercury poisoning is frequently alkaline, even in the absence of alkaline therapy. The cause of this alkalinity may lie at any one of three different levels; in the tissues, in the bladder and lower urinary tract, or in the kidney. The lowered tension of the alveolar CO₂ can be accepted as proof of an acidosis of the blood and also presumably of the tissues. The low ammonia coefficient absolutely rules out the presence of a cystitis with an ammoniacal fermentation of the urine. It is quite possible that the kidney is the principal factor in the production of these anomalous results. In health the kidney is more permeable to acid than to alkali, and secretes an acid urine from an alkaline blood. In chronic nephritis this permeability to acid is definitely impaired,²⁹ more and more acid radicals are retained in the body, and eventually an acidosis is set up. Under such conditions, however, an acid urine is the rule, and not one of alkaline reaction. The lesion in the "sublimite" kidney is quite unlike that seen in chronic nephritis. The damage is confined almost entirely to the tubular elements, and there are large deposits of the alkaline earths, in which calcium salts predominate.³⁰ It is possible that in some stages of the intoxication such a kidney might be relatively impermeable to acids, but still permeable to bases, with the result that an alkaline urine might be excreted, even in the presence of a mild acidosis. This suggestion is advanced merely as an hypothesis to explain the presence of an alkaline urine at a stage of the disease when other findings pointed to a definite condition of acidosis.

With the return of a normal kidney function all signs of acidosis disappeared.

SUMMARY.

1. The necessity of prolonged and vigorous treatment of every case of bichloride poisoning cannot be too strongly emphasized. Many apparently moribund individuals have been saved by properly directed, and vigorously pushed therapeutic measures. Death should be the only indication for a discontinuance of treatment prior to the complete recovery of the patient.

2. Retention of waste nitrogen is undoubtedly a factor in the early fatal issue of these cases. There are rarely any signs of uremia. The protein sparing powers of the carbohydrates

²⁷ Levy, Rowntree and Marriott: *Arch. Int. Med.*, 1915, XVI, 389.

We are indebted to Dr. J. H. King for the determination of the alveolar CO₂ and to Dr. Levy for the estimation of the H-ion concentration of the blood.

²⁸ Pfeiffer: *Deutsch. Archiv. f. klin. Med.*, 1907, XC, 591.

²⁹ Palmer and Henderson: *Loc. cit.*

Howland and Marriott: *Loc. cit.*

³⁰ Heineke: *Loc. cit.*

Saikowski: *Virchows Arch.*, 1866, XXXVIII, 346.

are of the greatest value in delaying the appearance of the extreme grades of nitrogen retention which usually precede death. If carbohydrate cannot be retained by mouth, glucose may be given intravenously in a 10 per cent to 50 per cent solution. In addition to its protein-sparing action, the glucose itself acts as a mild diuretic.

3. It is probable that alkalis have a decidedly beneficial action. Macnider⁴ has recently pointed out that they are capable of protecting the kidney from the full effects of uranium intoxication. It is possible that large doses of sodium bicarbonate given intravenously soon after the taking of the poison would exert a similar protective action in bichloride poisoning. The diuretic action of the alkalis is well known.

4. There is a very close agreement between most of the functional tests. Closer examination, however, shows that tests of retention or of elimination alone do not reflect the actual state of renal function as accurately as do these tests, which compare the rate of excretion of various substances in the urine with the concentration of the same substances in the tissues of the body. The coefficient of urea excretion and the phthalein test can be depended on to give more accurate information regarding certain phases of renal function (the excretion of nitrogen and water) than can be obtained either from the determination of the level of the T. N.-P. N. in the blood or of the amounts of nitrogen excreted in the urine.

5. The specific gravity curve is a valuable index of renal function. Fixation of the specific gravity is seen only at the height of renal insufficiency. The variations in the concentration of the urine become more and more marked as renal function approaches normal.

6. The acute course of the intoxication is shown by the functional tests. Even after six days of anuria, the kidneys regained a practically normal functional capacity within 12

days of the reestablishment of urinary secretion. All trace of anatomical damage disappeared from the urine in less than three weeks.

7. The low value of the chlorides in the plasma explain the apparent retention of salt after the secretion of urine has been resumed. The retention is of the same general type as that seen in pneumonia. It is not due to any impermeability of the kidney to sodium chloride.

8. The lowered tension of the alveolar CO₂ would seem to indicate the presence of an acidosis during the early stages of the intoxication.

DISCUSSION.

DR. L. G. ROWNTREE: Just a word concerning this alkaline treatment, which is based upon the work of Macnider, whose results have not yet been published. During the summer he informed me that in uranium-poisoned animals the administration of bicarbonate of soda does away with the anuria which follows in these animals on the subsequent administration of an anæsthetic. He also found that some of his animals under alkaline treatment show very slight or absolutely no pathological changes following the ingestion of an amount of uranium capable of producing very striking pathological and functional changes when sodium bicarbonate is not used. The use of the alkali in this case was probably a very important factor in the recovery of the patient.

The lay press has very recently called attention to this alkaline treatment, which, it says, is being used with success in Cincinnati by Fisher in poisoning with bichloride of mercury.

DR. JANEWAY: In addition to the very great scientific interest of these studies on this patient, they emphasize the very great importance of proper treatment of cases of bichloride poisoning. These cases are so common nowadays that it is important for the medical profession to understand as well how to treat them as the laity now understand how to acquire the condition. It is equally essential that every hospital should be prepared to treat cases of bichloride poisoning properly immediately they are received. It is up to every practitioner either to know how to treat these patients or to get them promptly to the nearest hospital that does.

THE FOLLOW UP SYSTEM.

THE METHODS EMPLOYED UPON THE SECOND SURGICAL DIVISION OF THE NEW YORK HOSPITAL.

By FREDERIC W. BANCROFT, M. D., New York.

The compilation of statistics has been important in the advancement of medical and surgical knowledge. Nevertheless, full advantage has not been taken of the opportunities and possibilities in this respect. Buried in the dust in countless hospitals is the labor of innumerable hospital internes whose case histories contain much valuable information. Moreover, too often, memory alone has been depended upon for recording valuable data. However, in the last ten years the classification of histories and compilation of statistics, based thereon, have come to be valued increasingly. Yet one striking deficiency has prevailed—the late results of operations have not been recorded. In the last analysis the end results are the best guide for the surgeon. Codman of Boston was the pioneer in developing and emphasizing this feature. He has made an

active and widespread effort to stimulate hospital staffs to make and record post-operative observations.

The conscientious management of a surgical service demands not only a detailed knowledge of the immediate results of operative treatment, but also the ultimate or end results.

In general, until recently, only spasmodic attempts have been made to ascertain the results after patients have left the hospitals. Most surgeons are convinced that all patients should be followed for at least one year. Many patients, who are considered not of sufficient interest to trace, are often the very ones who present unsatisfactory late results.

Such a "follow up" system should prove of inestimable value to the patient, to the surgical staff, and to the hospital.

⁴ Macnider: Jour. Exp. Med., 1916, XXIII, 171.

A. ADVANTAGES TO THE PATIENT.

There are two main types of cases referred to a hospital for surgical treatment:

1. Those patients for whom operation is necessary to save life.

2. Those for whom operation is indicated to improve health and economic efficiency. It is to this second class that the data obtained from a follow up system are most important.

For instance, a patient suffering from hernia applies to a hospital for advice. He should be informed as to the percentage of risk that is attached to such an operation; how long he will have to remain in the hospital; how long it will be before he is able to perform his regular work, and how long it will be before he reaches the maximum efficiency. He should also be informed what percentage of cases recur. With these data he may make his decision in regard to the operation.

A woman who suffers from lacerations received at child-birth should know not only the immediate mortality of the operation, but also how long she will be confined to the hospital, how long it will be before she is able to perform her housework, and what effect the operation will have upon future pregnancy and delivery.

The study of the end results will aid the surgeon in the advice he gives the patient. He will recognize that all operations are not successful, and that in certain types of patients a given operation will succeed, while in others it will fail.

B. ADVANTAGES TO THE SURGEON.

The operative policy of a surgical service is directly dependent upon the study and analysis of the late results of operations. If it is found that a certain procedure is not giving permanent relief, it will stimulate the members of the staff to devise means that will improve the results.

In the year that this system has been in operation at the New York Hospital, it has been found that a certain number of patients, operated upon under the diagnosis of chronic appendicitis, have not been relieved of their original complaint. Certain members of the staff are now making a careful analysis of all cases diagnosed as chronic appendicitis, with the object of determining wherein lies the fault. Such a study can be made only by careful analysis of the histories, physical examinations, laboratory and X-ray data, operative findings, and the *end results of a large series of cases.*

C. ADVANTAGES TO THE HOSPITAL.

In the reduction of the number of cases returning for secondary operations and the reduction of the number of surgical complications, such as sepsis, phlebitis, cystitis, etc., lies an excellent means for utilizing hospital funds for the care of the greatest number. A bed may be monopolized for months by a single patient with local sepsis, which otherwise would be occupied by several patients in rotation. Every patient day lost in a charitable hospital, by these complications, should be multiplied by the daily per capita expense. In the weekly discussions described later, all cases of infection, sepsis, etc., are discussed and methods are sought for their prevention in the future.

We have found occasionally that dissatisfied patients have left the hospital and have gone elsewhere for treatment; but upon receipt of our postals and letters they have returned, and in many instances we have been able to correct their erroneous impressions. Every cured and satisfied patient leaving the hospital is an asset, every unimproved or dissatisfied patient is a liability.

Before discussing the details of "The Follow Up System," I wish to mention the weekly conferences held by the second surgical division. These include the report of the return "Follow Up" cases for the previous week. This review is essential for the improvement of the work of the surgical organization.

Once a week grand rounds are conducted by Dr. Pool, the attending surgeon, with the staff and clinical clerks. Every case is dressed. The treatment of the wounds is discussed and a permanent record made on the bedside charts of the condition of each patient and wound. Following the rounds, a conference is held by the entire staff, including attendants and internes. A full discussion is encouraged in regard to—

A. Details of the cases noted on rounds. Many questions bearing upon the progress of the case; the diagnosis or operation may call for discussion either of an explanatory or of a critical nature.

B. A detailed, tabulated report and discussion of the operative results of the preceding week. (*Cf. below.*)

C. Diagnostic errors of the preceding week.

D. A detailed, tabulated report and discussion of the end results in the return cases examined on the previous Sunday.

Let us consider topics B, C and D in detail:

B. OPERATIVE RESULTS.

The operative cases of the week are discussed; unfavorable results and unfavorable developments are analyzed, and an effort made to determine the cause of any unsatisfactory condition. The poor results are tabulated as advised by Codman as follows:

1. Errors due to lack of technical knowledge or skill (E-s).
2. Errors due to lack of surgical judgment (E-j).
3. Errors due to lack of diagnostic skill (E-d).
4. The patient's enfeebled condition.
5. The patient's unconquerable disease.
6. The patient's refusal of treatment.
7. The calamities of surgery, or those accidents and complications over which we have no control.

For example: In the permanent records, sudden and unexplained deaths are marked as surgical calamities (S-c). Infections and hematomas as errors of surgical skill (E-s).

C. THE DIAGNOSTIC RECORD OF THE WEEK IS THEN CONSIDERED.

Errors of diagnosis (E-d) are referred to the operator for explanation, and a general discussion of the case follows. This is an extremely important feature of the work. It is believed that such an analysis and discussion will lead to greater care in arriving at a correct and exact diagnosis before operation.

will emphasize diagnostic mistakes, and call attention to means of avoiding them in future cases.

To obtain an exact diagnostic record, we employ the following method: The anæsthetist, prior to the beginning of each operation, records the ante-operative diagnosis on the anæsthesia chart. The operator is entitled to record his diagnosis up to the time of making his initial incision; after that it cannot be changed. At the end of the operation a revised diagnosis is recorded.

In the cases in which the diagnosis at the close of the operation is still in doubt, as in tumors, and in some cases with acute abdominal symptoms where no lesion has been found, final decision as to diagnosis is deferred until it is determined by the course of the case, or by the pathologist's report.

D. THE RESULTS IN THE CASES WHICH HAVE BEEN EXAMINED ON THE PREVIOUS SUNDAY MORNING ARE ANALYZED.

Those recorded as "fair" and "poor" are discussed, and, if necessary, the original histories of the cases are reviewed. The cause of failure is sought and a plan for avoiding similar failures in the future is considered. The errors or failures are grouped according to the classification given above in section C.

A follow up system, to be effective, must be so adapted that it automatically follows for at least one year all cases leaving the hospital, and, in certain selected cases, for a much longer period of time.

The present system is so constituted that all patients on leaving the wards are requested to return for observation at the end of three months; if at that examination there is no need for earlier observation, they are requested to report again at the end of nine months. In this manner all cases are followed for at least one year.

The forms used are modelled, with slight variations, after those designed by Corscaden of the Presbyterian Hospital, New York. His work in this direction cannot be too highly commended.

NEW YORK HOSPITAL. SECOND SURGICAL DIVISION. FOLLOW-UP SYSTEM.

1. Each morning the charts and bedside cards of the patients to be discharged that day are gathered by the stenographer from the wards. The names and numbers of the patients are entered on card A. These are filed alphabetically.

2. Card B is then filled out for each patient, with his name and number on one side, and the date and hour at which he is to return for examination on the other. These are then attached to the bedside cards and sent back to the wards to be given to the patients on their departure.

In filling out card B, the date upon which a patient is to return for examination is figured out approximately three months from the date of discharge. As each attending has certain Sundays in each month when he is on duty, the patients operated upon or treated by him are requested to return on those Sundays.

3. The name and number and date of examination of each patient is then entered on card C, which is filed according to the date upon which the patient is to return.

4. The data for filling out card D and its carbon copy E is taken from the chart and bedside card of each patient discharged. This is done every Monday morning for the discharges of the previous week.

Card D is then filed numerically.

Card E is attached to card C in the calendar file.

5. At the end of each week, card C and sheet E of all patients due to report on the following Sunday are taken from the calendar file, placed alphabetically in boxes, and sent to the examining room.

A red signal is placed on the corresponding master sheet D in the numerical file to signify that the carbon copy of the case has been sent to the examining room. This signal is removed on return of sheet E and card C.

If the patient has returned for examination, the master sheet is then filed away numerically and the date card filed according to the date upon which he is to return the second time. If the patient did not return for examination, a yellow signal is placed on the master sheet, signifying that a letter is to be written requesting the patient to return the following Sunday. If he returns, the master sheet is filed away numerically. If, however, he does not come to this second appeal, a green signal is applied to the master sheet, signifying that the case has been reported to the Social Service.

6. As each patient comes up for examination on Sunday morning, the examining doctor makes note of his observations on card C, also the approximate time of the patient's next return.

7. The day after the examination the boxes are returned to the filing room. The doctor's notes of his examination on card C are then typewritten on the inside of the master sheet D and its carbon copy E in the space marked F.

A new card C is made out with the patient's next date of examination. The old card C is destroyed.

C and E are then filed again under the next return date on the calendar file.

The master sheet D is returned to the numerical file.

When the folder F is filled, it is torn off and inserted in the original history of the patient, and a new folder placed in the numerical file.

8. Each Monday a postal card G is sent out as a reminder to all patients due to report the following Sunday.

9. A letter H is sent to the patients who did not return for their first examination.

A yellow signal is placed on the master sheet D in the numerical file, signifying that a letter has been sent to the patient. These signals are removed when the patient reports or when the case is given to the Social Service.

The following Sunday the carbon sheet E and card C of all patients to whom letters have been sent are included in the cases sent down to the examining room.

10. If the patients to whom letters have been sent do not report in a week's time, either by letter or in person, the card C

CARD A.



CARD B.

Please come to the hospital and bring this card with you
on

at.....

If you change your address send your new address to

Second Surgical Division

NEW YORK HOSPITAL

8 West 16th Street

New York City

(OVER)

Name

CARD E.

No.

We are asking you to return to see us for a few minutes in order that we may carefully watch the result of your treatment in the hospital.

By so doing we may advise you as to any treatment that may be necessary, and at the same time complete the records of your case.

If you will show this at the office of the hospital at the time written on the other side of this card you will be directed to the Doctor whom you are to see.

(OVER)

Form 259

NAME

HISTORY No.

DATE OF EXAMINATION

CARD C

DATE TO RETURN

Name	Age	M. W. S.	Date of Admission	Date of Discharge	Hosp. No.
------	-----	----------	-------------------	-------------------	-----------

Addr. of Pat.

MASTER SHEET D

Name and Addr. of Pt's Phys.

Name and Perm. Addr. of Frnd

Preop. Diag.

Post-op. Diag.

Came for relief of

Operator

Anes.

Operation

Condition of wound

Compl. of
Convales.

Path. No.

POSTAL CARD G.

NEW YORK HOSPITAL

8 WEST 16th STREET

Will you return to the Hospital on Sunday.....
 at.....A. M., as we desire to note the progress of our patients after
 they leave the hospital. Advice will be given you in regard to your
 condition.

Bring this card with you. If you cannot come, please write.

.....
 Attending.

Dear Doctor:

CARD I.

The following cases operated upon or treated by you are due to report on:

NAME

DIAGNOSIS

TREATMENT

HISTORY No.

Surgical Record Clerk.

and the sheet E are sent to the Social Service nurse, the case to be investigated by her and the patient induced to report for examination if possible.

When the case is given to the Social Service nurse a green signal is placed on the master sheet, which is removed on the receipt of a report from the Social Service nurse or return of the patient.

11. The attending surgeon receives a list (Card I) of the patients operated upon or treated by him, who are due to report for observation.

WEEKLY REVIEW OF CASES.

Sunday morning was chosen, because it is the day on which most people of the working class are free. The patients are requested to report at 9.30 a. m. One of the attending surgical staff, three internes, and the Social Service nurse, employed for the follow up system, are in attendance. The two junior members of the interne staff take histories of the cases. In order to include the important facts of the history, an outline is furnished with the history cards.

POST-OPERATIVE HISTORY.

1. Local Condition: Pain. Function.
2. Economic: Ability to do full amount of work; and how soon after discharge.
3. General Condition: Comparison of before and after operation. Did the operation or treatment cure the trouble? Weight—loss or gain?
4. Body Functions: Appetite. Digestion. Bowels. Urination. Menstruation. Marital.

The attending surgeon on duty and the house surgeon then examine the patients and make notes upon card C of the Follow Up System, as described above. Immediately following the physical examination, a note is written on the card tabulating the case as "good," "fair" or "poor." It is from this tabulation that the analysis is made for the discussion at the weekly conference.

HELP EMPLOYED FOR SUCH A SYSTEM.

During the year 1915 there were 1344 patients admitted by the Second Surgical Division. One stenographer is employed by the staff; she carries out all of the clerical work of the Follow Up System; besides this, she typewrites the operator's descriptions of all operations.

SOCIAL SERVICE.

When no response has been received from either the postals or letters, the case is referred to the Social Service Department, which has assigned the nurse to trace these cases. Her success depends, to a large extent, upon her energy and ingenuity. In New York, people living in tenements and boarding houses move frequently, and it is often difficult to find them. It may be necessary to determine their nationality and their religion—the nearest church of that denomination will often yield the information desired; or it may be sufficient to inquire

from neighboring stores or saloons. If the nurse is persistent, her percentage of returns will be relatively high. If she is unable to persuade patients to return for examination, it is her duty to record whatever information she can acquire.

Now in regard to the practical *modus operandi* of the system, we have found that the personal element is important. If the house surgeon interviews the patients at the time of discharge, and impresses upon them the fact that they may be benefited by the examination, a large number will report. If they return once, they will usually return in response to a second request. In fact, they will often come for examination when not expected, because of some ailment. The following is a report from February 1, 1915, to December 1, 1915:

REPORT OF THE FOLLOW-UP SYSTEM FROM FEBRUARY 1 TO DECEMBER 1, 1915.

Cases to return.....	808	
Cases returned on first request.....	399	or 49%
Cases returned from letters.....	87	
Patients reported by letter.....	87	
No. of cases returned and heard from.....	573	or 70%

SOCIAL SERVICE.

Cases given to Social Service.....	228	
Return of patient.....	64	or 28%
Report from nurse.....	70	or 30%
Not found by nurse.....	90	
No. of cases returned and reported upon.....	134	or 58%
Total No. of cases returned.....	550	or 68%
Total No. of returned, heard from and reported upon by Social Service.....	707	or 87%

In order to demonstrate the efficiency of the system, we have reviewed the cases of simple inguinal hernia operated upon between February 1, 1915, and September 1, 1915. A complete review would be out of place here.

Let us, however, consider, for example, the economic factor: There were 120 patients with hernia operated upon; of these, 108, or 90 per cent, were traced. Mention was made of the patient's ability to work in 96 cases, or 89 per cent. No note was made in 12 cases, or 11 per cent.

Of these 96 patients:

Eighty-four, or 87.5 per cent, were performing their usual work at the end of three months.

Nine, or 9.4 per cent, were performing light work.

Three, or 3.1 per cent, were unable to work.

Twenty-two patients gave definite data of how soon they went to work after leaving the hospital:

2	went to work in	1	week after discharge.
9	" " " "	2	weeks " "
1	" " " "	3	" " " "
1	" " " "	4	" " " "
3	" " " "	6	" " " "
2	" " " "	8	" " " "
2	" " " "	10	" " " "
2	" " " "	32	" " " "

In reviewing our cases diagnosed as chronic appendicitis, we found that a considerable number were not relieved in regard to their original complaint.

In order to study these cases, we have adopted a more elaborate history form and complex physical examination. As time goes on it is very probable that certain forms of histories and physical examinations will be developed for different types of cases, so that in studying the late results of a series of cases there will be adequate data for extensive research. Our main error in the first months of the system was a tendency to write insufficient histories and inadequate physical examinations.

In closing, I wish to thank the staff of the Second Surgical Division for the privilege of presenting this report.

The organization of the system was largely due to the efforts of Dr. Pool and Dr. Turnure.

DISCUSSION.

DR. WINFORD SMITH: Dr. Bancroft referred to Dr. Codman of Boston. I had the pleasure of hearing Dr. Codman speak recently on the subject of the End Result System, and whenever you have the opportunity of reading what Dr. Codman has to say about "end results" I strongly recommend that you do so. It is inter-

esting reading and presents some facts that bear thinking over carefully.

We have passed through the sanitary stage in hospitals—the stage when we were all more or less sanitary mad. I have about come to the point of view that we are now going through that stage with regard to the use of the term "efficiency." There is one danger, it seems to me, in the general adoption of follow-up systems. Without in any way meaning to reflect upon the system as outlined by Dr. Bancroft, which has, I think, great merit and which I have observed working most successfully, I do think we ought to bear in mind that it is a very easy matter to be carried away by the advocates of efficiency methods and to install follow-up systems for this or that subject. If a follow-up system collects statistics and data which enable us to know where mistakes have been made, or to devise a better technique, or to finish a job which we had thought was finished, then it is valuable. But a great many of these systems, as I have known them, have been established merely with the idea of doing something in the line of efficiency, and have collected a great mass of statistics, some useful and much of them useless, with the latter obscuring the former. That sort of follow-up system is not of much use, and before we or any other hospital adopt one like it, we should work it out very carefully in its application to our own individual purposes, just as it has been worked out to suit the needs of the New York Hospital. I am sure the society owes Dr. Bancroft a vote of thanks for presenting such an interesting and instructive paper.

WILLIAM BUDD, PIONEER EPIDEMIOLOGIST.*

By ASSISTANT SURGEON-GENERAL W. C. RUCKER, M. S., M. D., GR. P. H.,

United States Public Health Service, Washington, D. C.

So many notable additions to the knowledge of medical science have been made in recent years by laboratory workers that many of us have fallen into the habit of thinking that all medical discoveries must have the microscope and the test-tube as their point of origin. This is in part true, in so far as it relates to the causal agents of disease and their effects upon the body of man and the lower animals, but just as the practice of medicine depends upon knowledge gained at the bedside, so the science of epidemiology rests upon observations made during the spread of disease. When the practice of medicine forsakes clinical study for laboratory investigation the human element is lost. When we limit epidemiological study to the four walls of a laboratory, the scope of its vision becomes narrowed, and facts which could have been gained by personal contact with disease pass unobserved. Not every one has a laboratory at his command, and relatively few have the training which is requisite for good laboratory work, but every physician, no matter what his position nor where he may be located, may conduct valuable epidemiological investigation, if he will but observe what is going on around him. Jenner, the country doctor, gave to the world a sure prophylactic against smallpox. Another country practitioner, working without a laboratory and before the birth of bacteriology as a science, gave to us so clear an outline of the epidemiology of typhoid fever that it still stands as a model and with a few minor additions would summarize our knowledge of the disease.

William Budd, practitioner of medicine, careful student and logical thinker in the science of epidemiology, was born in September, 1811, in North Tawton, a town on the borders of the beautiful Dartmoor in Devonshire, England. He was the fifth son of Samuel Budd, being one of nine brothers, seven of whom entered the medical profession and became leading practitioners. The family was one of great talent. Five sons graduated at Cambridge. Four of these were fellows of their respective colleges, and all were wranglers. Four of Dr. William Budd's nephews likewise became fellows of colleges in the same university. Both Dr. William Budd and his older brother, Dr. George Budd, the author of the great work on "Diseases of the Liver," were fellows of the Royal Society.

The Budds were descended from Jean Budd, a baron during the time of Charles the Great. As a reward for his military service, Jean Budd was given a domain on the Norman seacoast. His descendant, William Budd, founded the town of Rye, and during the Norman invasion of France he housed the King. His descendant, Richard Budd, had four sons, three of whom became sailors and subsequently settled in the town of Rye in Sussex County, England. John Budd, who succeeded to the barony, came over at the time of William the Conqueror and landed at Rye, where his relatives were then living. He distinguished himself during the Norman invasion of 1066, and married a sister of William the Conqueror. He subsequently became the Earl of Sussex. The family intermarried with the Nevils, the Brownes, and the Montagues, and it was from this distinguished stock that William Budd, the subject of the present sketch, was descended.

* An address delivered before The Johns Hopkins Historical Club, Baltimore, Maryland, on March 13, 1916.

With his eight brothers, William Budd was educated in the home of his father, himself a surgeon of no mean ability. In 1827, when he was 16 years of age, he went to Paris. There he studied for four years under Louis Andral, Cruvelhier and Broussais in the Collège de France and the École de Médecine, and, under the tuition of Broussais, first became acquainted with the intestinal lesions of typhoid fever. While in Paris he contracted typhoid, and the leeching and starvation, which was the accepted treatment of the disease at that time, was carried to such a point that he was unable to pursue his studies for several years. In spite of this, he valued bleeding very highly in the early part of his career. Returning from Paris, he continued his medical studies in London and Edinburgh, and subsequently became a pupil of Sir Thomas Watson at the Middlesex Hospital. This is the "Sir T. Watson, Bart.," to whom Budd dedicated his *opus magnum*, "Typhoid Fever, Its Nature, Mode of Spreading and Prevention," "in grateful remembrance of many encouraging words."

In 1838 Budd took the M. D. degree from the University of Edinburgh. His graduation thesis was on "Rheumatism," and secured for him a gold medal. The essay clearly foreshadows the views which he expressed three years later in his paper before the Royal Medical and Chirurgical Society on "Diseases Which Affect Corresponding Parts of the Body in a Symmetrical Manner." This justly famous paper (*Medico-Chirurg. Trans.* 1842, XXV, 100-166) produced a profound impression. Watson (*Principles and Practice of Physic*, 3rd edition, p. 694) says that it throws "a strong light upon this perplexed subject, and brings the phenomena, not only of gout, but also of many other important complaints, within the operation of one general, comprehensive and intelligible law." It is interesting to note that on the same evening that Budd's paper was presented, a highly philosophic essay on "The Relation between Symmetry and Disease" was read by no less person than the illustrious Sir James Paget.

After graduation Budd served for a short time as physician to the seamen's hospital ship *Dreadnaught* at Greenwich, but was compelled to resign his post because of an attack of typhus fever of which he almost died. In 1839, during his convalescence, he resided with his brother, Dr. Richard Budd of Barnstable, and prepared an essay on "Fever," in competition for the Warneford prize of £50. He failed to receive the award, however, because the judges, of whom Sir John Forbes was umpire, were of the opinion that the ideas enunciated in his essay were "too novel and startling."

This is not at all surprising, the medical world at that period being divided into camps, each busily engaged in pursuing its pet theory of disease spread. Brigham, in his "Treatise on Cholera," published at Hartford, Connecticut, in 1832, reflects accurately the beliefs of the times. Speaking of the contagiousness of cholera, he says:

Upon this delicate and difficult subject medical men are much divided. They may be divided into three classes who hold to different opinions:

1. The first, though least numerous class among the intelligent medical men, are the exclusive contagionists, who believe that the cholera is communicated from an unhealthy body to a sound one,

by approximation, or actual touch. To this class belong also the great mass of the non-medical community—the civil authorities of towns and those who have the power to make and enforce quarantine regulations; regulations which, as regards the prevention of cholera, have been of no use, but, on the contrary, as facts fully exhibit, have been productive of immense evils.

2. A larger class are the anti-contagionists, who believe that the cholera depends either on a general cause everywhere existing, or arises from numerous causes, the most powerful of which are, exposure to cold and humidity at night, and burning heat during the day, the abuse of stimulating liquors, bad food, want of cleanliness, etc.

Some suppose it is produced by the magnetic influence of the earth, the telluric power. Others think the disease is primitively nervous, and depends on an electro-magnetic cause.

3. A third, and probably an increasing class, are those who keep to a middle course, between the contagionists and the anti-contagionists, and believe in what is called the doctrine of contingent contagion. These say that, although the disease arises from some aerial or terrestrial influence of which we at present know nothing, and over which we have no control, yet in the filthy hovels of the indigent, in the impure air of crowded apartments, the disease may, and sometimes does, acquire a character of communicability, which it did not at first possess, and of which it is deprived when these circumstances are not present, or when it occurs in well ventilated and cleanly situations.

In the hands of the great Murchison, the anti-contagionist theory that filth was the generator, not the vehicle, of disease was moulded into a dogma to which was applied the name of the Pythogenic theory. In a paper presented to the Royal Medical and Chirurgical Society in 1858, Murchison said:

In the course of this essay I shall bring forward what I consider positive proofs that this fever (typhoid) is produced by emanations from decaying organic matter, and I would, therefore, suggest for it the appellation of "pythogenic fever."

Charles MacLean, in his work, "Evils of Quarantine Laws and Non-Existence of Pestilential Contagion" (London, 1825), voices perhaps the views of the leading men of the profession at that time:

The existence of contagion in epidemic diseases is not a question which is now to be proposed for solution. It is already solved. To regard it as problematical or uncertain and disputable, as the pestilential contagionists still do, or affect to do, is to be ignorant of much of what has been done and written on the subject. The impossibility of the existence of contagion universally, in epidemic diseases, is a principle which I have, in various works and upon various occasions, already established upon an immovable foundation.

In the face of such opinions, it is not remarkable that the observations of Budd, then in his 28th year, should receive but scant consideration and that he should labor for more than 10 years on the problem and die long before his beliefs acquired any very general acceptance.

In 1839 Budd returned to North Tawton and entered into practice with his father, and here began those intensive studies which were to be the basis of his work on "Typhoid Fever, Its Nature, Mode of Spreading and Prevention," published over 30 years later. In the introduction to this volume he paints a word picture of the environment in which he then found himself, an environment which is almost duplicated by that of many of the country practitioners of America:

In the early part of my professional life, while engaged in country practice in Devonshire, outbreaks of typhoid fever continually fell under my eye, amid conditions singularly favorable to the study of its origin and mode of dissemination.

Of these outbreaks, the most memorable occurred in the village of North Tawton, where I then lived.

In addition to the advantages enjoyed by country practitioners generally, in the observation of such events, there were others peculiar to the position I then occupied.

Having been born and brought up in the village, I was personally acquainted with every inhabitant of it; and being, as a medical practitioner, in almost exclusive possession of the field, nearly every one who fell ill, not only in the village itself, but over a large area around it, came immediately under my care.

For tracing the part of personal intercourse in the propagation of disease, better outlook could not possibly be had.

At the date of the outbreak in question, the people of the place numbered some eleven or twelve hundred souls.

Of these, a small minority, consisting chiefly of women and children, worked in a serge factory. The rest were employed in agricultural pursuits.

The spot on which the community dwelt is richly endowed with all the natural conditions of health. Built on a dry soil, in the midst of an open and well-drained country, and occupying the side of a hill sloping gently to the northwest, this village had long been justly noted in that part of Devon for the rare healthiness of its site.

What is more to the present purpose is, that it had for many years enjoyed an almost entire immunity from the fever to which it was so soon to pay so large a tribute.

This is the more to be remarked, because there were in the economy of the place, and in the habits of the people, many things which, according to modern views, are hard to reconcile with such a fact. In the first place, there was no general system of sewers. A few houses, occupied by the more opulent, were provided with covered drains, but all these might be counted on the fingers. In the cottages of the men who earned their bread with their hands, and who formed the great bulk of the inhabitants, there was nothing to separate from the open air the offensive matters which collect around human habitations. Each cottage, or group of three or four cottages, had its common privy, to which a simple excavation in the ground served as cesspool. Besides this, it was a part of the economy of all who worked in the fields, as indeed of many more, to keep a pig, one of whose functions was to furnish manure for the little plot of potatoes which fed man and pig alike. Thus, often hard by the cottage door there was not only an open privy, but a dungheap also.

Nevertheless, these conditions existed for many years without leading to any of the results which it is the fashion to ascribe to them.

Much there was, as I can myself testify, offensive to the nose, but fever there was none. It could not be said that the atmospheric conditions necessary to fever were wanting, because while this village remained exempt, many neighboring villages suffered severely from the pest. It could not be said that there were no subjects, for these, as the sequel proved, but too much abundance.

Meanwhile privies, pigstyes and dungheaps continued, year after year, to exhale ill odors, without any specific effect on the public health.

Many generations of swine innocently yielded up their lives, but no fever of this or any other sort could be laid to their charge. I ascertained by an inquiry conducted with the most scrupulous care that for 15 years there had been no severe outbreak of the disorder, and that for nearly 10 years there had been but a single case.

For the development of this fever a more specific element was needed than either the swine, the dungheaps, or the privies were, in the common course of things, able to furnish.

In the course of time, as was indeed pretty sure to happen, this element was added, and it was then found that the conditions which had been without power to *generate* fever, had but too great power in promoting its spread when once the germ of fever had been introduced.

On July 11, 1839, a first case of typhoid fever occurred in a poor and crowded dwelling. Before the beginning of November, in the same year, more than 80 of the inhabitants had suffered from it under my care.

In this environment Budd was able to study the disease in all of its manifestations and to correlate the going and the coming of those who were affected with it. He realized fully the opportunities which the situation offered, and wrote many years later:

Where the question at issue is that of the propagation of disease by human intercourse, rural districts, where the population is thin, and the lines of intercourse are few and always easily traced, offer opportunities for its settlement which are not to be met with in the crowded haunts of large towns.

As a result of his observations at this time he came to the conclusion that the fever was essentially a contagious or self-propagated disease. Yet despite his high enthusiasm in this belief, Budd fully realized that many convincing proofs must be brought forward before his views would be very generally accepted. In 1866 he prefaced his pamphlet on cholera by saying:

I speak still in the interrogative mood, because, however strong the evidence may seem, one is almost afraid to believe in so great a triumph as this, until it is assured by more extended experience. In exact proportion to the importance and magnitude of any given conclusion, the true philosopher, strong though his own conviction may be, is exacting of proof.

In order to appreciate fully the radical nature of such a conclusion, it is necessary to understand the doctrine which was generally accepted at that time. In the Manual on the Practice of Medicine, by Dr. Tanner, which at the time of the publication of Budd's work in 1873 had already reached its sixth edition, the author, in speaking of the doctrine of typhoid fever as a contagious disease, chiefly disseminated through the excreta of typhoid patients, calls it "an elusive hypothesis." The Physician's Vade Mecum, at that time a standard work, dismisses the doctrine with the statement that "observed facts and the few experiments which have been made tend to disprove these views." Elsewhere in the work, the authors, Guy and Harley, state:

Much doubt prevails whether enteric fever be infectious or not. The question really turns upon the existence of a distinct specific organism. Positive proof that it may be conveyed from one person to another is wanting, and certainly the majority of people affected with the disease derive it from the clearest evidence from one and the same source. Those in attendance upon persons suffering from enteric fever sometimes fall ill of the disease, but the source of the disease may be present in the house.

Not only did Budd decide that the disease was contagious, but he came to the conclusion that it was of a specific nature. And in 1873 he clearly prophesied the existence of the bacillus which was not discovered until some seven or eight years later. He said:

It is humiliating to think that issues such as these should be contingent on the powers of a creature so low in the scale of being that the mildew which springs up on decaying wood must be considered high in comparison.

He also came to the conclusion, from the foregoing, that typhoid fever not only propagates itself, but that it propagates no other kind of fever. This was widely at variance from the views at that time held by those who believed in the pythogenic theory of the disease, and as evidence on this point he clearly recognized the period of incubation of the disease, the immunity conferred upon those who had had the disease, and the fact that not all persons living in the same environment contracted the disease.

Very early in his studies Budd recognized that the intestinal discharges played the major rôle in the dissemination of typhoid, and he deduced therefrom:

1st. That as a rule this fever will spread the more, the less perfect the provisions for preventing the discharges from the human intestine from contaminating the soil and air of the inhabited area.

2d. That where these provisions fulfil this end, the disease will show little or no contagious power.

3d. That its tendency to run through families will oftenest take effect where there is only a common privy, least often where there is a well-appointed water-closet. That this tendency will be observed very commonly, therefore, in country places, and comparatively rarely amongst the wealthy inhabitants of large towns.

4th. That, generally speaking, the distribution of the disease will be different in country and in town: that in the country, where there are few or no sewers, and where, consequently, the intestinal discharges accumulate around the infected dwelling, the disease will occur in a thickly clustered manner; that in the town, where these discharges are conveyed, often for long distances, by sewers, the ramifications of which extend through large communities, it will appear in a more scattered form.

5th. That, as what the sewer receives from the fever patient is incomparably more virulent than anything else thrown off by him, the infection (until the true interpretation of the events be known) will appear, for the most part, *as if it had its source in the sewer, and not in the already infected man.*

6th. That in the country, the contagious nature of the fever will be obvious and unmistakable; but that in the town, it will most commonly be masked and obscure.

7th. That in the former, the fever will be epidemic and thickly clustered; in the latter, as a rule, endemic and scattered.

8th. That separation of the healthy from the infected will be of no avail to prevent the spread of the fever, unless it include separation from the intestinal discharges also.

9th. That, for this reason, the severest outbreaks will be seen in schools, barracks, and other large establishments, where a single common privy is often, alike, the receptacle of the discharges from the sick, and the daily resort of large numbers of healthy persons.

In the course of his studies—studies which he never relinquished until forced by the hand of age—he early came to the

very logical conclusion that the pollution of water supplies was the great factor in typhoid transmission. In fact, Budd recognized all the media of transmission now known, with the possible exception of flies. In his work on typhoid he says:

One mode of communication has attracted little attention, which it is important, nevertheless, not to overlook; I speak of the tainted hands of those who wait on the sick. Among the poor, and in ways that will suggest themselves, and need not be more particularly described, there is reason to believe that this mode often has a large share in spreading the disease through the family circle. Passing from the hand to other things under contingencies that are not only very conceivable, but are sure now and then to occur, the contagion thus arising may sometimes have a much wider scope. I possess evidence which renders it in the highest degree probable that milk and butter, especially, may become infected in this way.

He clearly recognized the occurrence of milk outbreaks, and in one of his writings thus lays emphasis on the danger of raw milk:

All risk may be abolished by *boiling* the milk, however deeply it may be polluted. Drinking unboiled milk is like eating raw meat, and is open to consequences of the same pathological order. I have no doubt that, if all milk were boiled before being used, a marked diminution in the prevalence of more than one very serious type of the disease would soon follow.

As preventive measures, Budd at all times laid strong emphasis on the disinfection of the discharges of the sick, the isolation of all typhoid patients, the careful and frequent washing of the hands of the attendant, and the boiling of the drinking water. Truly, as he says, "These are golden rules; where they are neglected the fever may become a deadly scourge; where they are strictly carried out, it seldom spreads beyond the person first attacked."

Budd is described by his contemporaries as a strong, hardy looking man of robust body, good height and brave presence. This powerful body, which in his younger days bespoke in every movement the invigorating air of his native Dartmoor hills, housed a mind which was sensitive and emotional almost to a fault. An intimate said of him that he "was possessed of a heart tender as a woman's and gentle as a child's." His energy and industry were unbounded, and the catholicity of his interests was remarkable, almost overwhelming in his later years. That he should be a skilled physician was to be expected. He had been reared in a medical atmosphere and carefully trained both in Great Britain and on the Continent. When he entered practice he was 27 years of age, and when he was 30 his well-matured mind had already arrived at conclusions which at first startled and later modified the views of the medical profession. His practical knowledge of disease, particularly of the communicable diseases, was very great, and included the contagious diseases of cattle, sheep and pigs, as well as those of human beings. His observations on the diseases of animals were very valuable, and in 1863 he published a pamphlet on "Variola Ovis, Sheep's Smallpox; or the Laws of Contagious Epidemics, Illustrated by an Experimental Type." He also studied a disease of swine which he called "pig-typhoid." Rinderpest, or cattle plague, also claimed his attention, and, when the disease first appeared in England,

Budd held emphatically that the only way to stamp it out was to slaughter the animals as soon as they showed symptoms of the disease. His recommendation of "a poleaxe and a bit of quicklime" at first met with great ridicule, particularly at the hands of the *London Times*, but his views were ultimately and very successfully adopted.

His accurate knowledge of French, German and Italian kept him abreast of the medical advances of the Continental schools, while his facile pen led him far into the field of medical literature. He was a skilled artist and a good photographer, accomplishments which were of great assistance to him, particularly in the production of his work on typhoid fever.

In 1841 he removed from North Tawton to Bristol, and speedily assumed a high position among his colleagues. He became physician to St. Peter's Hospital in 1842; physician to the Bristol Royal Infirmary in 1847, and for many years held the chair of medicine in the Bristol Medical School. At the Infirmary he found the pathological museum, which had been started by Robert Smith. With characteristic energy he began the collection of specimens and aided materially in the up-building of the museum. Largely through the championship of Tyndall, who proudly proclaimed himself one of Budd's disciples, he was elected a fellow of the Royal Society—"a rare honor for a provincial medical man" (1870). Tyndall wrote of him:

Dr. William Budd I hold to have been a man of the highest genius. There was no physician in England who, during his lifetime, showed anything like his penetration in the interpretation of zymotic disease. For a great number of years he conducted an uphill fight against the whole of his medical colleagues, the only sympathy which he could count upon during this depressing time being that of the venerable Sir Thomas Watson.

Budd's typhoid studies naturally led him to entertain similar views regarding the transmission of cholera. He held that the contagious agent was present in the dejecta and that by a proper disinfection of all the stools in all the cases, an outbreak of cholera could be suppressed. He applied this method to the eradication of the Bristol cholera epidemic in 1866, with such success that although the disease was introduced at 26 different points in the city, and in severe form, only 29 cases occurred, whereas in 1849 there were 1979 cases.

Dr. Budd says of this epidemic ("Cholera and Disinfection, or Asiatic Cholera in Bristol in 1866," 1871):

Whatever the light by which we view the events, we are thus unavoidably led to the belief that this city (Bristol) owes its exemption from an epidemic of cholera, in the summer of this year (1866), to the specific measures taken to prevent the spread of the malady. Had the principle on which these measures are founded been purely empirical, the facts would have left us no reasonable alternative. But, as we know, the case is far otherwise. By an induction, which for commanding clearness and logical severity is rare indeed in physic, we have arrived at the conclusion that Asiatic cholera is propagated extensively, as I believe, by the rice-water discharges. To destroy these discharges is, therefore, to destroy the seed by which the disease is sown, and, by the very act, to prevent the possibility of a future crop. In Bristol the seed has been destroyed and the crop has failed. What was expected has exactly come to pass. The accordance between theory and fact is not general merely, but very nearly perfect.

The relationship between Budd's work and the cholera investigations of Snow is very interesting. It has been held that to Dr. John Snow belongs the credit for the anti-cholera work, and that Budd added nothing material to the subject. Budd himself was most emphatic in his praise of "Dr. Snow's admirable, long prior, and entirely original researches." The facts, however, are these: Snow proved that cholera was frequently disseminated by drinking water, a discovery the importance of which cannot be overestimated. Budd, however, proved that by the disinfection of the discharges and the isolation of the sick, the pollution of the water could be prevented and the disease checked. So strongly did he believe in the necessity for a full supply of pure water, that he was one of the most zealous promoters of the Bristol waterworks.

Budd was never content to follow the beaten paths, and in his scientific work he exemplified Ptolemy's *dictum* that "He that would follow philosophy must be a freeman in mind." His active brain led him into speculations regarding most of the epidemic diseases, and while the pressure at which he lived left little opportunity for extensive writings, he prepared several short notes which were published, and several longer manuscripts that were discovered after his death, but were never printed. On one occasion he gave a friend, a medical officer about to go to Jamaica, very careful instructions for preventing the spread of yellow fever, and subsequently published these with considerable additional matter in the *Lancet* (April 6, 1861, I, 337). He was firmly convinced that the disease was spread by the excreta and he, therefore, focused his eradication measures on the disinfection of the discharges of the sick and the sterilization or destruction of things with which patients had been in contact. In his article "On the Contagion of Yellow Fever" he says:

Whenever a contagious disorder is attended with discharges that are characteristic of it, these discharges are always (as I have elsewhere endeavored to show) the chief vehicle of the morbid poison. They originate, in fact, in, and are the outward mark of, the very act of elimination. It is from this intimate connexion with the specific poison, in each particular case, that such discharges derive their specific character. I need scarcely add that yellow fever offers no exception to this law.

From the lofty heights of our present knowledge we may be tempted to smile at this positive statement, but we should bear in mind that up to 1901 similar views were held almost universally, and that at the time Budd wrote many still believed yellow fever to be non-communicable. His views were, of course, entirely academic, as he never saw the disease.

This cannot be said of his observations on tuberculosis. In his profession, which up to the time of his retirement was enormous, he had ample opportunity to study this disease both in its clinical and epidemiological aspects. The results of these studies appears in the form of a "Memorandum on the Nature and Mode of Propagation of Phthisis," which appeared in the *Lancet*, October 12, 1867 (page 451). This communication was made in an original and somewhat unusual way. This may best be explained by quoting the letter which G. E. Paget addressed to the *Lancet* on September 31, 1867, by way of an introduction to Budd's paper:

To the Editor of the *Lancet*:

SIR: The paper I send enclosed was received by me last December, in a sealed packet from Dr. W. Budd of Clifton, with a request that I would take charge of it until he should direct me to break the seal. At his desire I opened the packet a few days ago, and I now send you the contents, requesting the favor of their early publication in the *Lancet*. They are an epitome of what Dr. W. Budd has been for some time intending to publish in a more complete form; but his intention has been frustrated, and is still delayed, by the engrossments of professional practice and other circumstances beyond his control.

You will at once perceive the originality of his views and their very high importance, if established. If the evidence now given of their truth be incomplete, it is at least abundantly sufficient to raise them out of the mere hypothesis and ensure their careful consideration by pathologists.

In a letter to me Dr. W. Budd says, "I have strong reason for believing that my views on tubercle, with certain qualifications, apply to cancer also."

Budd's communication was simple and plain, but reflected in every line the intensity with which he had attacked the problem. He says:

The following are the principal conclusions to which I have been led regarding phthisis or tubercle:

1st. That tubercle is a true zymotic disease, of a specific nature, in the same sense as typhoid fever, scarlet fever, typhus, syphilis, etc., etc., are.

2nd. That like these diseases tubercle never originates spontaneously, but is perpetuated solely by the law of continuous succession.

3rd. That the tuberculous matter itself is (or includes) the specific morbid matter of the disease and constitutes the material by which phthisis is propagated from one person to another and disseminated through society.

4th. That the deposits of this matter are, therefore, of the nature of an eruption, and bear the same relation to the disease, phthisis, as the "yellow matter" of typhoid fever, for instance, bears to typhoid fever.

5th. That by the destruction of this matter on its issue from the body, by means of proper chemicals or otherwise, seconded by good sanitary conditions, there is reason to hope that we may eventually, and possibly at no very distant time, rid ourselves entirely of this scourge.

Time and space forbid the inclusion of the evidence on which he arrives at these conclusions. He says, however, that the idea of the communicability of tuberculosis occurred to him when he was taking a walk "in the second week of August, 1856." He remarks:

The long interval which has occurred between the summer of 1856 and the present time (1867) has been occupied in collecting data bearing on the question raised by this new theory—in accumulating evidence of various kinds and in examining and carefully weighing difficulties. I earnestly hope that they will not be too lightly rejected. At any rate, I can say that they have not been brought forward in haste or without due deliberation. I have, in fact, considerably exceeded the ten years which, with a fine sense of what is due to such an enterprise, the Roman poet prescribed as the time to be given to every composition intended by the writer to endure.

Laboratory studies and further epidemiological investigations have proven the correctness of Budd's conclusions—conclusions which are the more remarkable because they were made on clinical observations unsupported by experimental

evidence and 15 years prior to the discovery of the tubercle bacillus.

His deductions on "Scarlet Fever and Its Prevention" (*British Medical Journal*, January 9, 1869, 1-23) might pass as the current views of to-day. He recognizes the value of disinfection and isolation, and decries the practice of frequent fumigation, which was then the accepted practice. He says:

There is good reason to believe that not only the eruption on the skin, but everything which is shed by the body of the infected, is heavily laden with the germs or seeds by which (alone, no doubt) the disease is propagated. The discharges from the throat and nose are, I imagine, especially virulent.

William Budd is described by his contemporaries as an eloquent orator—logical and gifted in debate. He was absolutely fearless in expressing the opinions which he held, yet ever modest and conservative. He clearly stated the results of his observations and made the deductions therefrom with logic and philosophy. In the British Medical Association, particularly in the Bristol branch, he occupied a leading place, and no aspect of medicine failed to attract the attention of his alert and energetic mind. His public health activities were unceasing. He acted as adviser to the Bristol health authorities, and on his own initiative investigated many epidemics of typhoid elsewhere and outlined the measures for their eradication. He issued, on several different occasions, pamphlets on the measures to be adopted for the prevention of the spread of typhoid fever and cholera, directions which would suit the needs of to-day very well. In his teaching and dispensary work he was ever busy; in fact, the accounts of his life show him to have been a man of such boundless capacity for work that his life was shortened by his indefatigable industry.

But to this incessant mental and bodily activity there had to be an end. He resigned the chair of the Practice of Medicine in the Bristol Medical School, and in 1862 gave up his appointment at the Bristol Royal Infirmary. Holidays in Germany and Switzerland would temporarily restore him to health, but his scientific energy was so unbounded that he would re-attack his work with such vigor that he would again break down. He suffered from agonizing headaches and his one desire was to complete his work on typhoid fever. This he did in 1873, and was immediately hurried away to France for rest and change. He returned to England in much worse health, and became (according to Clarke—*British Medical Journal*, 1880, I, 163-166) "partially hemiplegic." He died at Clevedon, on Friday, January 9, 1880, in his seventieth year. Early in life Budd married a Miss Hilton, a member of a well-known family in Kent, and had many children, by some of whom and his most devoted wife he was tenderly nursed until his death.

Budd's lasting contribution to the science of epidemiology may best be summed up in the summary of his book on typhoid fever. Other researches he made, to be sure, but many of these were contingent on his typhoid studies; studies which brought us nearer to the absolute prevention and eradication of this disease than the work of any other observer, either before or since his time. It, therefore, seems fitting that the words

which closed the *opus magnum* of his life, words which in reality closed the book of his scientific labors, should be the final chapter in this story of that pioneer epidemiologist, William Budd. The labors of a lifetime, and the ambitions of his career, are summed up in the following propositions:

1. That typhoid fever is, in its essence, a contagious or self-propagating fever, and is a member of the great natural family of contagious fevers, of which smallpox may be taken to be the type.

2. That the living body of the infected man is the soil in which the specific poison, which is the cause of the fever, breeds and multiplies.

3. That the reproduction of this poison in the infected body and the disturbance attaching to it constitute the fever.

4. That this reproduction is the same in kind as that of which we have, in smallpox, ocular demonstration.

5. That the disease of the intestine, which is its distinctive anatomical mark, is the specific eruption of the fever, and bears the same pathological relation to it which the smallpox eruption bears to smallpox.

6. That, as might have been anticipated from this view, the contagious matter by which the fever is propagated is cast off, chiefly, in the discharges from the diseased intestine.

7. That, as a necessary result, sewers and the cloacæ which, under existing sanitary arrangements, are the common receptacles of these discharges, are also the principal instruments in the transmission of the contagion; and, consequently, that in many instances the infected sewer, and not the infected man, appears as if it were the primary source of the specific poison.

8. That once cast off by the intestine, this poison may communicate the fever to other persons in two principal ways—either by contaminating the drinking water, or by infecting the air.

9. That, as an inevitable consequence of the impalpable minuteness of the contagious unit, and the many invisible and untraceable ways in which it is transmitted, cases must be constantly occurring, exactly as in the other contagious fevers, whose linear descent cannot be followed, and which spring up, therefore, under the semblance of spontaneous origin.

10. That the occurrence of such cases obviously constitutes no proof whatever that this fever ever does arise spontaneously.

11. That the exceeding speciality of the conditions attaching to the reproduction of the specific poison in the living body itself, as well as the facts relating to the geographical distribution, past and present, of this and the other contagious fevers, constitute evidence as strong as such evidence can ever be that none of these fevers originate spontaneously, but are propagated solely by the law of continuous succession.

And lastly—to crown the whole induction by a practical test—that by destroying the infective power of the intestinal discharges, by strong chemicals or otherwise, the spread of the fever may be entirely prevented, and that by repeating this process in every fresh case as it arises the disease may in time be finally extinguished.

In arriving at these conclusions, I would observe:

That the principal data on which they rest are, to the best of my belief, sure. Where these data consist in events observed by myself, I can vouch for their accuracy; where in events reported by others, I have taken, whenever this was possible, the most conscientious pains to verify them. In addition to this, all the great cardinal facts are distinguished in a peculiar degree by that precision and exactness which fit them alike for scientific statement and severe scientific deduction.

Whether the inferences drawn from the facts be logical, or whether, consistently with the laws of logic, any other inferences can be substituted for them, it is for others than myself to determine.

The whole induction is gradual. There are no great leaps, but the argument is conducted step by step; and I have striven to the utmost throughout to make one step sure before attempting the next.

The theory, in its entirety, is not only simple and harmonious, but it is in strict accordance with what we already know, of a certainty, of other members of the same family group.

Above all, its truth may be tested every day by a practical test, the employment of which can do no harm, and may do incalculable good.

Here I might fitly conclude. With this last step, as all may see, science passes into duty.

At this very hour scores of English homes are the scene of the agonizing anxieties with which recent experience has made the nation familiar. In hundreds, or, if we extend our view to the whole of Europe, in thousands, of cases, these anxieties have been consummated, within the month, by the death of the sufferer.

And all of this the work of an ignoble thing, which, if what has gone before be true, may be disarmed of its terrors by the simplest of precautions.

In my introductory remarks I endeavored to show, by illustrations drawn chiefly from the homes of the poor, how deeply humanity is concerned in the eradication of this fatal pest.

Since those remarks were first written (1859) the extension of its power to persons more conspicuous in rank has succeeded in awakening and directing, in a very striking way, the national attention to it. More than once since that time men or women bearing great historic names have fallen victims to it. Twice it has cast its dark shadow on the throne. Once it has placed the entire nation in mourning; and once again it has brought the entire nation, on bended knee, to the throne of grace in thanksgiving for a happier issue.

That the people of this kingdom should testify, in this most solemn of ways, their deep sense of responsibilities they have in this matter is well.

But if they wish to set a seal on the sincerity of their piety, there is—I say it with all humility—a still higher attitude to take.

It is, to spare from this hour no human effort to put under foot this great enemy of man. And let no one suppose that this is a matter in which he has no personal interest. The duty itself we may evade, but we can never be sure of evading the penalties of its neglect. This disease not seldom attacks the rich, but it thrives most among the poor. But by reason of our common humanity we are all, whether rich or poor, more nearly related here than we are apt to think. The members of the great human family are, in fact, bound together by a thousand secret ties, of whose existence the world in general little dreams.

And he that was never yet connected with his poorer neighbor, by deeds of charity or love, may one day find, when it is too late, that he is connected with him by a bond which may bring them both, at once, to a common grave.

DISCUSSION.

DR. HEND: I should like to call General Rucker's attention to the fact that Nathan Smith was a country practitioner in Vermont and New Hampshire between 1820 and 1830. He also studied typhoid fever, and said he had been familiar with cases for a number of years. He was strongly of the opinion that typhoid fever was contagious and was transmitted from one person to another. He had very clear ideas on the subject. I mention this to show another example of the opportunities afforded to the country practitioner to study disease.

DR. FORD: Dr. Rucker's paper is one of great interest from a number of different standpoints and raises several points for consideration. In the first place, it seems to me that we should not attribute to such a county as Devonshire an ignorance which

is in any degree comparable to the ignorance which occurs in some of the backward parts of the United States. The county of Devonshire has an extremely interesting medical history. As far back as 1767, Dr. George Baker investigated the disease called Devonshire colic and palsy, and made probably the first definite contribution to our knowledge of industrial diseases, in that he was able to show that this colic and palsy in Devonshire was lead colic. Devonshire even at that time was noted for its milk and cider, the cider being highly prized in London. The people in Devonshire suffered greatly from colic and palsy, and it was not until George Baker went there and found that leaden vessels were employed in the manufacture of cider, and that Devonshire colic was lead colic, did the world have a correct idea of this condition.

It might be added that the Exeter Hospital is one of the oldest in England, having been established in the early part of the 18th century. Devonshire was also the seat of the first investigations upon the scientific disposal of sewage. The Cameron tank was discovered by a Scotchman who settled in Exeter. In modern times we have had a number of men from Devonshire who took a prominent part in the advancement of medical science in England.

In this country also we had a number of early observations upon cholera. Daniel Drake published his book on Epidemic Cholera in 1839. He enumerates all the causes which can be hypothesized for cholera, such as telluric influences, emanations from decaying matter and from infectious discharges. Although he saw several hundred cases of cholera during the years 1831-1833, he yet failed

to grasp the essential thing in the constant association between new cases and old cases.

In Germany Pettenkofer, who occupied the stage especially from 1866 to 1886, which was the period shortly after Budd's final work in typhoid fever, was apparently not influenced in any way by Budd's observations. He always maintained that the material given off from a cholera or typhoid patient was not in itself infectious. That is the essential difference between the conclusions reached in Germany and by Budd and his followers in England. Pettenkofer maintained that this material must undergo a process of ripening in the soil before it is infectious and capable of communicating disease. Herein Budd stands as the great pioneer in the development of the science of epidemiology. It is of significance that when Koch developed bacteriology he at once came to the views concerning the epidemiology of disease which Budd had advocated.

It seems to me that it is especially interesting that whereas countries like Germany, Austria and France were for so many years unable to get rid of typhoid fever, England succeeded in doing it almost completely. For the last 20 years they have had only isolated cases. Sir Robert Boyce, who came over some years ago to investigate yellow fever, was surprised to learn how many cases of typhoid existed here. England, under the lead of men of the clearest wisdom of Budd, has been able to eradicate typhoid fever, just as it has smallpox, by carrying out the strictest possible measures suggested by such individuals. In this country at the present time, and also in France and Germany, we are much behind England in this respect.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

MARCH 6, 1916.

1. Some Newer Methods in Rectal Surgery. (Abstract.) DR. HARVEY B. STONE.

Dr. Stone presented informally a report of three procedures that are comparatively new and that he has been employing for the past several years.

(a) *Sacral Anæsthesia*.—This method was first introduced as a technique by Cathelin of Paris in 1902, but was first used for surgical anæsthesia by the Germans, notably Stoessel and Schlimpert. In this country it has been employed by Lynch of New York, and Bransford Lewis of St. Louis. The technique was described and a needle for the purpose of introducing a fluid was demonstrated. The needle is introduced into the sacral canal from below through the sacral hiatus. The fluid used is novocain in one per cent solution, which has been found more satisfactory than other substances experimented with. From 80 to 100 cc. have been employed. Good surgical anæsthesia is obtained by this method, but certain constitutional disturbances, as evidenced by rapid pulse rate and mental confusion, are met with occasionally. No ill after-effects were observed in the comparatively small number of cases in which this form of anæsthesia was employed by Dr. Stone and Dr. Hebb. In some cases the method is not feasible because of the difficulty in introducing the needle for anatomical reasons, and, in a small percentage of the cases in which the introduction is accomplished successfully, satisfactory anæsthesia fails to develop. The method thus offered, however, is a valuable aid to operation in the class of patients who would not be fit subjects for general anæsthesia, and who are suffering with conditions about the rectum and perineum not well adapted for the employment of local anæsthesia.

(b) *Report of a Method of Treating Pruritus Ani by the Injection of Alcohol*.—A paper will be published in the BULLETIN dealing with this subject in detail.

(c) *A New Operation for the Treatment of Recto-urethral Fistula*.—Dr. Young and Dr. Stone have operated upon seven cases of this exceedingly distressing and intractable condition with excellent results in every case. The older methods have been so unsatisfactory that the good results, so far obtained by the newer procedure, make its wider employment desirable. The method may be summarized as follows. First, the establishment of a suprapubic cystostomy to permit the drainage of urine away from the repair of the fistula. Second step, a midline incision in the perineum to the anterior margin of the anus, and a circular incision about the mucocutaneous margin of the anus. Through this incision the perineum is exposed, the sphincter ani muscle is divided in the midline anteriorly, and the rectal mucosa is dissected upward all around as in an exaggerated Whitehead operation. This dissection is carried upward so as to divide the fistulous tract, separating the rectal orifice from the urethra; and the rectum is then loosened from all its attachments above this point sufficiently far to permit the drawing down and out of the portion containing the rectal orifice of the fistula. The dissected bowel is then amputated through healthy tissue above the level of the fistula. The opening in the urethra is closed by sutures on a sound. Third step, repair. The perineal structures are brought together with sutures from side to side so as to separate the rectum from the urethra. The sphincter muscle is repaired. The stump of the bowel is sutured to the circular part of the skin incision, as in a Whitehead operation. The midline incision in the perineum is repaired with interrupted sutures.

2. The Pathogenesis of Thyroid Intoxication. DR. H. S. PLUMMER, Rochester, Minn.

DISCUSSION.

DR. L. F. BARKER: One cannot listen to anyone who has had such a large experience with exophthalmic goitre as Dr. Plummer has had without being deeply interested. I spent two days at

the Mayo Clinic in October last, most of the time with Dr. Plummer, and I was much interested in the kind of study going on there, especially in his careful statistical study of the cases.

It is necessary to understand the terms Dr. Plummer uses and to relate them to the terms in the bibliography, if we are to grasp the exact relation of the cases he describes to the cases that have been reported. You will notice Dr. Plummer speaks of hyperplastic goitre and non-hyperplastic goitre as two great subdivisions. By further subdividing, he describes the toxic and the atoxic forms of non-hyperplastic goitre. In the first place, this terminology is based upon pathological anatomy, but from his clinical experience he is able to correlate the clinical pictures with the pathological histology. In a very large number of cases, over 3000, he and his group of workers have been able to say beforehand from their clinical experience what cases belong to each group. That is indeed a remarkable clinical achievement.

Dr. Plummer uses the term "exophthalmic goitre" as practically synonymous with "hyperplastic goitre," as I understand him. Exophthalmic goitre is for him always a hyperplastic goitre. Non-hyperplastic toxic goitre is for him never "exophthalmic goitre." There is where his use of terms differs somewhat from the classifications used in the literature, inasmuch as for most writers "exophthalmic goitre" is used as a term synonymous with "Graves' syndrome," "Basedow's syndrome," and "hyperthyroidism." In other words, Dr. Plummer says that in "non-hyperplastic toxic goitre," there may be degrees of intoxication at times that yield symptoms which are almost indistinguishable from the symptoms that result from the intoxication in "hyperplastic goitre," or what he calls "true exophthalmic goitre." I think the difference in terminology is chiefly this—that Dr. Plummer reserves the term "exophthalmic goitre" for this one condition, namely hyperplastic goitre and its accompanying symptoms, a condition that runs a typical course clinically; whereas, the terms "Graves' disease," or "Basedow's disease," and for many the term "exophthalmic goitre," have been used in a wider sense to include not only "hyperplastic goitre," but also his "toxic non-hyperplastic goitre." If one keeps clearly in mind his use of terms, it is easy to follow Dr. Plummer's descriptions. Otherwise, one might be a little confused by trying to correlate his conceptions with those of contemporary medical literature.

One of the best things coming out of Dr. Plummer's work, it seems to me, is the very careful following of the course of these thyreopathies over long periods, by means of an analysis of records of careful observations. A thorough anamnesis is supported by "follow-up" records of the cases. Just as "jaundice" has, through the years, come to be subdivided into a series of conditions, so it would not be surprising if the *omnium gatherum* known as "Graves' disease," as "Basedow's syndrome," as "exophthalmic goitre," or as "hyperthyroidism" should be subdivided into a series of somewhat different conditions. This is what Dr. Plummer is trying to do, and he is giving names to the different members of the series and trying to differentiate them, so that we can all recognize them. I think this a very promising work and a kind for which we must all be grateful.

Much should be said about the theories advanced regarding the pathology of these conditions, the mode of action of the toxic substances upon the cells of the body, and the theories concerning iodine. These are all interesting topics and I should think that the ideas advanced may well serve as stimuli to a great deal of experimental work. As I understand it, they are to be regarded at present as simply working hypotheses, and we shall have to await results of experimentation before we can profitably discuss them at length.

Dr. GOETSCH: I was very much interested in hearing what Dr. Plummer had to say in regard to the association between the histological picture and the clinical syndrome in thyroid disease.

I do not know just what criteria Dr. Plummer has used with regard to the histological picture, but if they are the same as those which have been used during a good many years past, they are based largely upon the amount of colloid present in the thyroid, in the height of the epithelium and in the amount of hyperplasia generally of the alveolar cells. In general this association is undoubtedly true, for the large amount of colloid goes with the inactive type of thyroid. A small amount of colloid and a great amount of hyperplasia, a very cellular gland, go with marked hyperthyroidism.

There are a certain number of cases, however, in which this association does not hold. That is, there will be cases with a marked hyperthyroidism, in which, basing one's opinion upon these criteria, one would say the condition was not active. It is these cases that are difficult to explain upon the older histological basis. The index of the activity of the gland, therefore, will have to be based upon other than these criteria. In other words, one must know what the individual cells of the gland itself are doing. One can only determine this when the histological methods are so developed that there will be better criteria of activity than those previously accepted. Recently Dr. Bensley, of the University of Chicago, has developed a method by which he can demonstrate certain histological characteristics in the cells themselves which point to activity. The mitochondria are structures which are present in all cells and are present in numbers proportionate to the activity of the cell. For example, a cell which is undergoing active secretion or any cell which gives other evidences of activity, has a large number of these mitochondria present. If evidence of activity is associated with increased mitochondria content, then, when one is able to demonstrate increased mitochondrial content, one has a good basis for the assumption that these cells are active. When one applies these methods to certain cases of thyroid adenomata, we do find a very rich content in mitochondria. One has reason to feel that these cells with abundant mitochondria are active and are responsible for the symptoms present in these cases.

Then there is the adenoma with the capsule quite different from the surrounding thyroid tissue from which it can be shelled out without difficulty, the rest of the thyroid presenting every evidence of being normal. These cases show symptoms of typical hypertrophy, and when one examines a section of tissue taken from the thyroid surrounding one of these adenoma, and then the adenoma itself, one finds a striking difference in them, the normal thyroid presenting very few of the mitochondria and the adenoma cells being abundantly filled with them. It is well known that when one shells out one of these adenomata, symptoms subside rapidly.

In regard to the poisoning of the system. This is very interesting also. The thyroid toxæmia is undoubtedly the cause of the symptoms which the patients present. Just a word with regard to the effect upon the nervous system. Certain of these patients will show symptoms referable to activity of the sympathetic or autonomic nervous systems. It is interesting to see a patient come back after previous operation and to test her with the drugs which are calculated to stimulate one or the other of these systems. Recently I had occasion to examine a patient Dr. Halsted had operated on two years ago. She had forgotten altogether what her former symptoms were and she did not realize how much she had improved. When she received 10 mm. of adrenalin, she at once was transported back two years to her former condition. She said: "I feel now exactly like I felt each day two years ago. I realize now how much I have improved." This seemed to indicate that the thyroid secretion had an influence upon the syndrome which the adrenalin had in this instance. Similarly with the autonomic system, one can apply measures to bring out certain reactions which the patients show.

The hypertrophied gland does not merely secrete an abnormal amount of normal secretion. This is possibly the reason that the

symptoms are so varied. Moreover, it has been found that histologically there are structures present in the abnormal gland which are not present in the normal gland. If we can demonstrate histologically certain secretion antecedents in the hypertrophied cells that are not present in the normal ones, we have a certain basis for believing that we are dealing with a pathological secretion.

MARCH 20, 1916.

1. Case of Auricular Flutter. DR. C. H. GODDARD.

The case of auricular flutter to be shown to-night is of interest owing to its comparative rarity, and because of certain other exceptional features.

The patient, W. S., white, male, aged 61, came to the medical dispensary on March 14, 1916, complaining of shortness of breath. The history yielded the following points of interest.

At the age of 21 he had an attack of unconsciousness, which came on after he had run a considerable distance. It lasted for about two minutes, and left him none the worse for the experience. For 25 years there were no recurrences, but finally, 15 years ago, while working as a carpenter on a scaffold, he suddenly became faint and dizzy. Calling to a fellow workman, he collapsed, unconscious. This attack was again of about two minutes' duration, and was followed by no ill effects.

For three years he suffered no further inconvenience, but finally developed dyspnea upon exertion, accompanied by frequent attacks of unconsciousness similar to those already described. Eight years ago the dyspnea became so acute that he gave up his trade as carpenter, and became a night watchman. He nevertheless continued to have shortness of breath, and occasional attacks of unconsciousness.

One year ago he became a day watchman. This necessitated his being upon his feet most of the time, with the result that his dyspnea became aggravated, and five months ago he gave up his work, since which time he has been living quietly at home. His last attack of unconsciousness previous to admission occurred five weeks ago, following the exertion of moving a heavy piece of furniture.

Physical examination was negative with the exception of a rather extensive pyorrhea alveolaris, a moderate grade of emphysema, slight enlargement of the heart to the left, and a pulse rate of over 250. The urine was negative, and no signs of cardiac decompensation were apparent.

Further examination of the heart showed the P. M. I. to be in the fifth left interspace, $10\frac{1}{2}$ cm. to the left of the median line. The relative cardiac dullness extended $11\frac{1}{2}$ cm. to the left and 4 cm. to the right of the median line. The heart sounds were of a fetal character, and the rate, as counted with a stethoscope at the apex, was about 250. As nearly as could be ascertained by palpation, the same rate prevailed at the wrist. Tracings were accordingly taken upon a Mackenzie ink polygraph.

Upon laying the patient down in preparation for this procedure, the pulse rate suddenly fell very markedly, and, when counted at the wrist and apex, was quite regular at 84 per minute. The veins of the neck, however, showed a rapid and rhythmical succession of large waves, which, when counted upon the tracing, were seen to be at the rate of 252 per minute.

In the tracing, the time-marker at the upper margin is beating five times to the second. Below this is the radial tracing at a rate of 84, and lowest of all the venous tracing upon which the auricular or "a" waves appear at a regular rhythm of 252 per minute, or exactly three times that of the radial pulse.

A number of tracings having been taken, the patient was dismissed, to return the following day for admission to the hospital. As he arose from the couch, the præcordium began to heave, and palpation of the pulse showed that the ventricular rate was again

very high. A pulse tracing taken at once revealed a radial rate of 252. During the paroxysm the patient did not manifest any great discomfort, and dyspnea was not marked. He described this and other attacks as "a feeling as though his heart were running away with itself."

He returned next day as directed, and was admitted to a medical ward. A tracing taken upon him within an hour or two after his admission showed an auricular rate of 264, with a ventricular of 132.

This was on March 15th. The 2:1 rate persisted until the following afternoon, as demonstrated by further tracings. At this time he was given 1 mg. of strophanthin intramuscularly, at 4 p. m. A tracing taken two hours later showed an apparent bradycardia, the arterial pulse registering but 60 beats to the minute. This condition varied with that of tachycardia, while an apex tracing cleared the matter up, showing apex impulses at a rate of about 120. At times these all arrived at the wrist with equal force; at others they barely showed upon the radial tracing, while intermediate phases existed between these two conditions. Therefore, we had at times a pronounced example of the "Pulsus Alternans."

As the therapeutic procedure in these cases is to give large doses of digitalis and strophanthus in an effort to produce auricular fibrillation, which may, in favorable cases, revert to the normal rhythm, a course of infusion of digitalis, in doses of two drachms four times daily for a few days, was begun on the evening of the 16th. On March 17th, the day following the strophanthin treatment, he continued to show an alternating pulse in greater or less degree, the apex rate remaining quite regular and fairly rapid.

On the following day, March 18, his auricles began to fibrillate. The irregularity in the radial rhythm is graphically demonstrated in the measurements of the time intervals between beats (in hundredths of a second) shown below the tracings. This condition persisted until noon of the following day, at which time one set of tracings, showed auricular fibrillation, while a second, taken immediately thereafter, revealed a normal, regular pulse with a prolonged conduction time between auricle and ventricle, the "a-c interval" measuring about .28" instead of the usual .18"-.20". Following this, the patient relapsed into fibrillation, and has persisted in this condition up to the present time.

In these cases, the symptoms, which include palpitation, dyspnea, precordial distress, attacks of faintness, and sometimes even of unconsciousness, as in this case, are commonly followed by signs of cardiac decompensation. Some cases, however, go through attacks with little apparent discomfort and practically no signs of decompensation, as did this man. The danger lies in the fact that the continued rapid rate of the auricles, calling forth as it does very rapid ventricular contractions, may ultimately result in a profound embarrassment of the circulation, due to a weakening of the ventricular musculature under the unusual strain. The successful transformation of flutter into fibrillation, through active digitalis and strophanthus therapy, puts the heart in a condition where the ventricular rate may be readily controlled by the further administration of these drugs when necessary, and ordinarily results in a profound and rapid improvement in physical signs and symptoms. As the latter were not marked in this case, the onset of fibrillation of the auricles did not bring with it any marked change.

It is to be hoped that, therapy having been discontinued, the case will show itself to belong to that favorable group in which fibrillation is followed after a varying period of time by a normal rhythm, which persists. Other issues which commonly take place are: persistent fibrillation, relapse into flutter after a shorter or longer interval, and in some cases oscillations between auricular fibrillation, flutter, and normal rhythm. It is possible that oscillations between flutter and fibrillation existed during the early stages of fibrillation of the auricles in this case, as in some of the

tracings what appeared to be definite "a" waves appear upon curves where at other times no "a" waves are to be made out.

Care must be taken not to diagnose the onset of fibrillation in these cases from an irregular radial rhythm, without the support of other confirmatory evidence. This is due to the fact that the ventricles, instead of responding with regularity to every first, second, third or fourth auricular beat, as in this case, may respond successively now to the second, now the fourth, and now the third, and so on through many different combinations, giving a pulse that is irregularly irregular and hence very suggestive of fibrillation of the auricles.

It is to be noted that examination of the heart during the patient's stay in the hospital revealed no evidence of valvular defect. This makes for a favorable prognosis, which is admissible in such of these cases as present no evidence that the flutter is implanted upon lesions of valves or myocardium. The fact that the history indicates the probability that flutter has been present more or less constantly during the past 12 years, and the possibility that transient attacks of flutter occurred as long as 40 years ago, need also not militate against a satisfactory result. Cases are on record in which flutter has lasted for years, with ultimate recovery, while in others longer periods of years have elapsed, after the first appearance of symptoms, without serious injury to the patient.

2. Further Studies on the Schick Reaction and Practical Active Immunization Against Diphtheria. DR. WM. H. PARK, New York City.

3. Roentgenography as an Aid in the Localization of Cerebral Tumors. From a Study of 100 Cases. DRS. G. J. HEUER and W. E. DANDY.

To appear later in the BULLETIN.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

MARCH 13, 1916.

1. The Superstition and Folklore of Menstruation. DR. EMIL NOVAK.

To appear later in the BULLETIN.

2. William Budd, Pioneer Epidemiologist. DR. W. C. RUCKER, U. S. Public Health Service.

This paper appears in full in the current number of the BULLETIN.

THE LAENNEC.

MARCH 27, 1916.

1. The Influence of Certain Organic Substances on the Growth of the Tubercle Bacillus. DR. P. A. LEWIS, Philadelphia, Pa.

To appear later in the BULLETIN.

2. Experimental Meningitis. DR. C. R. AUSTRIAN.

To appear later in the BULLETIN.

NOTES ON NEW BOOKS.

A Clinical Study of the Serous and Purulent Diseases of the Labyrinth. By DR. ERICH RUTTIN. With a foreword by PROFESSOR DR. VICTOR URBANTSCHITSCH. Authorized translation by HORACE NEWHART, A. B., M. D. Cloth, \$2.00 net. (New York: The Rebmman Company, 1914.)

Dr. Ruttin was one of Politzer's assistants and is still connected with the University Clinic in Vienna. For many years this clinic has been particularly interested in the labyrinth and Dr. Ruttin's contributions, together with those of his associates Borony, Neumann, Beck, and Urbantschitsch, have entirely revised the old opinions concerning the physiology and pathology of the inner ear.

This volume has been very intelligently translated by Dr. Newhart and is invaluable for those interested in the functional tests of the hearing and vestibular apparatus, and in the pathology and therapy of the inner ear.

S. J. C.

A Manual of Diseases of the Nose and Throat. By CORNELIUS G. COAKLEY, A. M., M. D. Fifth edition. (Philadelphia: Lea & Febiger, 1914.)

This fifth edition of Dr. Coakley's manual, although in some respects an improvement on former editions, still leaves much to be desired from the point of view of the fourth year medical student.

Take for example the chapter on diseases of the tonsil. From it the student can get a very good idea of the clinical picture of a pharyngitis, acute tonsillitis and diphtheria, but only a very poor idea of the diagnosis of the chronic insidious infections of the tonsils, which are of so much importance in the etiology and treatment of many of the general systemic disorders—cervical adenitis, arthritis, digestive disturbances, renal lesions, anæmia, etc.

Furthermore, the advice concerning the operative procedures is not in accord with the principles of general surgery. This is particularly true in the directions given for controlling hemorrhage after the removal of the tonsils.

For the specialist, on the other hand, the book contains many valuable suggestions concerning the diagnosis and treatment of the common maladies of the throat and larynx.

S. J. C.

The Detection of Poisons and Powerful Drugs. By DR. WILHELM AUTENRIETH. Authorized translation by WILLIAM H. WARREN, PH. D. Cloth, \$2.00. (Philadelphia: P. Blakiston's Son & Co., 1914.)

This is the translation by William H. Warren, Professor of Chemistry in Wheaton College, of the standard laboratory manual on the detection of poisons, written by Wilhelm Autenrieth and now in its fourth edition. The best methods for the recognition of the various poisons are given in considerable detail and quantitative methods are elaborated for certain substances like arsenic, the presence of which in excess is evidence of crime. The book is well written, carefully translated, and will prove of great value to medical men interested particularly in legal medicine.

W. W. F.

Infant Feeding—Its Principles and Practice. By F. L. WACHENHEIM, M. D. Cloth \$2.00. (Philadelphia: Lea & Febiger, 1915.)

In recent years many books have appeared dealing with the feeding of infants and written for a professional audience. They aim to do two things, first, to give the methods employed for feeding infants in health and disease; and second, to point out the reasons why certain methods are advantageous and certain others disadvantageous, and to set forth the principles which should govern the choice of any one particular food or the variation of the different food elements. The first aim is usually well accomplished, the second very rarely so.

In this book the author discusses the various problems met with in feeding infants and gives methods and various formulae. The book reflects well the views of current authors, particularly those in Germany. These views are faithfully followed, even to

the employment of the unsatisfactory classification of Finkelstein for diseases of the gastrointestinal tract. The subject matter is presented in a concise but comprehensive manner, and the summary enables one to readily determine the facts essential for the successful feeding of infants. The book can be recommended as a practical handbook for infant feeding; it does not deal extensively with the principles of the nutrition of infants, but outlines the practice.

Lectures on the Heart. By THOS. LEWIS, M. D., F. R. C. P., D. Sc.
\$2.00 net. (New York: Paul B. Hoeber, 1915.)

In the autumn of 1914 Dr. Lewis visited America. The five lectures he delivered during his stay make up the small book entitled "Lectures on the Heart." In the first, the Harvey lecture in New York, he gives an excellent portrayal of the basic principles of electrocardiography, with a summary of the work that his laboratory has developed in the demonstration of the origin and course of "The Excitation Wave in the Heart." The next three lectures are those of the Herter Foundation, presented before the members of The Johns Hopkins University. The subjects are "The Method of Electrocardiography Exemplified"—an elementary discussion of the information acquired by the application of electrocardiography to the study of cardiac irregularities; "The Relation of Auricular Systole to Heart Sounds and Murmurs"—an interesting presentation of cardiophonography with a detailed discussion of auricular sounds and the different types of murmurs present in mitral stenosis; "Observations upon Dyspnea with Especial Reference to Acidosis"—a résumé, perhaps somewhat theoretical, of his latest experiments in the chemical laboratory on the diminished alkalinity of the blood with excess of non-volatile acids and acid salts, as an additional cause for dyspnea. The fifth lecture, on "Observations upon Cardiac Syncope," was given at the opening of the Faculty of Medicine at McGill. In this he groups the different causes of cardiac syncope and gives proof of the actual physiological and anatomical basis for such grouping. Besides their medical instruction, these lectures all emphasize a basis maxim held by Dr. Lewis—"the application of laboratory methods to questions of immediate and practical consequence."

It is rare that one has the opportunity to read so delightful a presentation, as Dr. Lewis here offers, of clear-cut scientific deductions. The combination of experimental research with accurate clinical observation, withal expressed so clearly and forcibly, is almost unique. Everywhere between the lines are numerous suggestions for those interested in this line of work. After reading the first lecture on the "Excitation Wave in the Heart," one despairs of finding a more stimulating experimental discussion with such sharply defined results. For this chapter alone every medical man should have this book.

E. W. B.

Infection, Immunity and Specific Therapy. By JOHN A. KOLMER.
M. D., Ph. D. pp. 870. Cloth, \$6.00. (Philadelphia: W. B. Saunders Co., 1915.)

This work is the most valuable one of its kind in English literature. The author has clearly stated the purposes of the volume: "First, to give practitioners and students of medicine a connected and concise account of our present knowledge regarding the manner in which the body may become infected, and the method in turn by which the organism serves to protect

itself against infection or strives to overcome the infection, if it should occur, and also to present a practical application of this knowledge to the diagnosis, prevention, and treatment of disease; second, to give to physicians engaged in laboratory work and special workers in this field a book to serve as a guide to the various immunologic methods; third, to outline a laboratory course in experimental infection and immunity for students of medicine and those especially interested in these branches."

It might seem at first sight that the accomplishment of these three purposes within one book would be a matter well-nigh impossible; yet even a casual review must convince one, not only of the author's complete grasp of the subjects under consideration, but also of his admirable clearness in the presentation of the various subjects he takes up. The book is divided into five main parts. Part 1 deals with general immunologic technique and includes descriptions of how to make suitable pipettes, the washing of blood corpuscles, methods for obtaining human and animal blood, the technique of animal inoculation and the preservation of the sera, etc.

Under Part 2 is included the general subject of infection and the principles governing it, so far as we know them.

Part 3 takes up the principles of immunity and immunological technique from the practical standpoint. Thus, in this section one finds admirable chapters on the opsonic index, the preparation of bacterial vaccines, agglutinins, antitoxins, complement-fixation reactions, anaphylaxis, etc.

Five chapters in Part 4 treat of the application of the principles of immunity in the prophylaxis, diagnosis and treatment of disease.

The last section includes a series of 60 different exercises designed to constitute a thorough course in experimental infection and immunity.

The book is essentially practical. Though the theoretical side of the various topics is well handled, greater emphasis has been laid upon the presentation of the application of the theory in practice. It would be very hard to pick out any one section which is better than another, for the reason that all the various methods are given a place in the book, the author's personal experience with reference to them is concisely stated, but in unbiased terms, and the proof of the superiority of this or the other method is left entirely for the reader or worker to prove for himself. A splendid feature of the book is shown in the frequent italicized sentences, which make it possible for the casual reader to pick out the points which the author is particularly anxious to emphasize. It should be pointed out that the author has in every case described the various tests and reactions in great detail, thus tending to secure accuracy, simplicity and definiteness. No particular attempt has been made to embody in the book all the literary references, but from time to time the more important ones are cited. Numerous well-colored illustrations, frequent tables, sample protocols of titrations, etc., play a large share in making the book a useful daily companion for the laboratory worker. There is also included an account of those immunologic, diagnostic reactions which have a direct bearing upon veterinary medicine. It is difficult to see how the book could be improved upon. It can, therefore, be recommended to students, physicians and laboratory workers as the one giving the best presentation of the subjects dealt with at present in existence in English literature.

S. R. M.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice; abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXVII is now in progress. The subscription price is \$2.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, \$2.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

BOOKS RECEIVED.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by Henry W. Cattell, A. M., M. D. Volume IV. Twenty-fifth series. 1915. 8°. 384 pages. J. B. Lippincott Company, Philadelphia and London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. Assisted by Leighton F. Appleman, M. D. Volume IV. December, 1915. 8°. 421 pages. Lea & Febiger, Philadelphia and New York.

The Adolescent Period: Its Features and Management. By Louis Starr, M. D., LL. D. 1915. 12°. 211 pages. P. Blakiston's Son & Co., Philadelphia.

The Physiology of the Amino Acids. By Frank P. Underhill, Ph. D. 1915. 12°. 169 pages. Yale University Press, New Haven; Humphrey Milford, Oxford University Press, London.

The Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Volume IV, Number 6. December, 1915. W. B. Saunders Company, Philadelphia and London.

A Text-Book of Physiology. By William H. Howell, Ph. D., M. D., Sc. D., LL. D. Sixth edition, thoroughly revised. 1915. 8°. 1043 pages. W. B. Saunders Company, Philadelphia and London.

Practical Cystoscopy and the Diagnosis of Surgical Diseases of the Kidneys and Urinary Bladder. By Paul M. Pilcher, A. M., M. D. Second edition, thoroughly revised, with 299 illustrations, 29 in colors. 1915. 8°. 504 pages. W. B. Saunders Company, Philadelphia and London.

Bone-Graft Surgery. By Fred. H. Albee, A. B., M. D., F. A. C. S. With 332 illustrations, three of them in colors. 1915. 8°. 417 pages. W. B. Saunders Company, Philadelphia and London.

Post-Mortem Examinations. By William S. Wadsworth, M. D. With 304 original illustrations. 1915. 8°. 598 pages. W. B. Saunders Company, Philadelphia and London.

Question Manual. Compiled by May Kennedy, R. N. 1915. 8°. 158 pages. Whitcomb & Barrows, Boston.

Oxford Medical Publications. Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following 4 volumes:

1. *A Guide to Gynecology in General Practice.* By Comyns Berkeley, M. A., M. D., M. C. (Cantab.), F. R. C. P. (Lond.), and Victor Bonney, M. S., M. D., B. Sc. (Lond.), F. R. C. S. (Eng.), M. R. C. P. (Lond.). 1915. 8°. 452 pages.
2. *Medical Lectures and Aphorisms.* By Samuel Gee, M. D. With recollections by J. Wickham Legg. 1915. 12°. 408 pages.
3. *Diseases of the Throat, Nose and Ear.* By William H. Kelson, M. D., B. S., F. R. C. S. (Eng.). 1915. 8°. 270 pages.
4. *Instinct and Intelligence.* By N. C. Macnamara, F. R. C. S. 1915. 12°. 216 pages.

Injuries of the Eyes, Nose, Throat and Ears. By Andrew Maitland Ramsay, M. D., F. R. F. P. S. (Glasgow), J. Dundas Grant, M. D., F. R. C. S. (Eng.), H. Lawson Whale, M. D. (Camb.), F. R. C. S. (Eng.), and Charles Ernest West, F. R. C. S. (Eng.). 1915. 16°. 160 pages. Oxford War Primers.

Report on the Medico-Military Aspects of the European War. From Observations Taken Behind the Allied Armies in France. By Surgeon A. M. Fauntleroy, U. S. Navy. Under the direction of the Bureau of Medicine and Surgery, Navy Department, Washington, D. C. 1915. 8°. 146 pages. Government Printing Office, Washington.

Interstate Commerce Commission. Twenty-Ninth Annual Report. Part I. 1915. 8°. 188 pages. Government Printing Office, Washington.

Saint Thomas's Hospital Reports. New series. Volume XLII. 1913. Edited by J. J. Perkins and C. A. Ballance. 1915. 8°. 205 pages. J. & A. Churchill, London.

THE INSTITUTIONAL CARE OF THE INSANE IN THE UNITED STATES AND CANADA.

BY

HENRY M. HURD, WILLIAM F. DREWRY,
RICHARD DEWEY, CHARLES W. PILGRIM,
G. ALDER BLUMER, T. J. W. BURGESS.

Edited by HENRY M. HURD, M. D.

The Johns Hopkins Press announces the publication of this important work prepared by a special committee of the American Medico-Psychological Association and published by authority of the Association in four volumes.

The work contains an authoritative account of the Care of the Insane from the earliest periods in the United States and Canada and is of great value to Physicians, Alienists, Hospital Officials, Charity Workers, and State, Public and Private Libraries.

Volume One contains an account of methods of care during the 19th Century in the United States and Canada and the growth of the law governing the insane. It contains 497 pages and many illustrations. (Now ready.)

Volume Two gives detailed and careful histories of individual Institutions in Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, and Missouri. (Ready, June 15.) About 900 pages with many illustrations.

Volume Three gives similar details of individual Institutions in Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, Wyoming; also in Alaska, the Hawaiian Islands, the Philippines and Porto Rico. (Ready, July 15.) About 800 pages with many illustrations.

Volume Four gives histories of individual Institutions in Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, Quebec and Saskatchewan; also in Newfoundland; also biographies of 200 philanthropists, hospital administrators or alienists; and index. (Ready, August 15.)

The price per volume, bound in cloth, payable upon publication, is \$2.50, or \$10 for the set; bound in leather, \$3.50, or \$14 for the set. The edition is limited and the price will be advanced January 1, 1917. Address

June 1, 1916.

THE JOHNS HOPKINS PRESS,
BALTIMORE, MD.

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BULLETIN

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ON THE VALUE OF ROENTGEN-RAY EXAMINATIONS IN THE DIAGNOSIS OF CANCER OF THE STOMACH.

By F. H. BAETJER, M. D.,

Associate Professor of Clinical Roentgenology, Johns Hopkins University and Hospital,

AND

JULIUS FRIEDENWALD, M. D.,

*Professor of Gastro-Enterology, University of Maryland School of Medicine and College of Physicians and Surgeons,
Baltimore, Md.*

It is a well-known fact that the diagnosis of cancer of the stomach is often exceedingly difficult, and especially is this true in regard to the early recognition of this affection. Even although the morbid process may have assumed considerable proportions, many of the important manifestations may still be absent, so that even at a relatively advanced stage a correct diagnosis, based upon the symptomatology, is often impossible. Any new method, therefore, which promises substantial aid in solving this intricate problem must be regarded as a very welcome addition to the means we already possess.

The X-ray has presented us with an additional method of diagnosis in the study of gastric cancer, and although like other methods of medical diagnosis which are not absolute, it is probably more correct than any of the other means for diagnosis which are common at the present day. Its findings, however, should always be taken in conjunction with the clinical findings before the final diagnosis is made.

In the X-ray study of cancer of the stomach, it is important, first of all, to recognize the varying positions and functions of the stomach under normal conditions.

The fundamental difficulty lies in the fact that the stomach is not a hard and fixed body; for we know that a perfectly normal stomach may present great variability, not only as to position, but also as to motility and the expulsion of its contents. As a matter of classification we may divide the various types of stomach into three classes—first, the stomach of the fleshy individual; second, the stomach of the medium-weight individual; and third, the stomach of the thin individual.

The three classes of stomachs differ very materially as to shape and position.

In the first group we are dealing with a high stomach, the pylorus lying to the right of the median line, well up under the gall-bladder region, and occupying an almost horizontal position. In the second group we have the stomach of the medium-

weight individual, which is generally cow-horn in shape, the pylorus resting in the median line, or just to the right of the spine. In the third group, we are concerned with the stomach of the thin individual, which lies to the left of the median line, and is generally prolapsed and fish-hook in shape, with the fundus well down in the pelvis. Associated with these various conditions, we have corresponding differences in the motility of the stomach.

It can easily be seen that, in the first two types, not only the motility, but also gravity aids in emptying the stomach, whereas in the third class we have gravity acting against its normal motility, inasmuch as the pylorus and duodenum are always from two to three inches above the fundus of the stomach.

We have no hard and fast rule, therefore, according to which we can say that the stomach must empty itself in a certain number of hours, and that, if this time be prolonged, we are justified in concluding that we are dealing with some pathological condition.

In the first class the stomach empties itself in about three hours; in the third class it takes about six hours. Hence the question of any beginning obstructive lesion is dependent very largely on the character of the stomach with which we are dealing. Another difficulty to be encountered lies in the fact that the motility of a normal stomach may be affected by conditions outside of the organ itself.

Consequently, in dealing with carcinoma of the stomach we cannot rely on the size, shape and position of the stomach or upon the retention of its contents. Our determination of the special lesion is dependent upon the study of two conditions, namely, the peristaltic waves of the stomach, and the many irregularities, or filling defects, in the organ itself. Unfortunately, as we have already noted, we possess no normal type of stomach from which we can draw comparisons; consequently, we are forced to determine the type of stomach that is normal for the individual undergoing the examination.

It is a well-known fact that the motility of the stomach is more or less affected by lesions in the organ itself, the degree to which it is affected varying according to the location of the lesion.

As a matter of classification, we may divide the carcinomatous lesions of the stomach into three classes: first, lesions in the cardiac end of the stomach; second, lesions in the body of the stomach not affecting the orifices; third, lesions at the pyloric end of the stomach. In each of these conditions the activity of the stomach is materially affected, but in quite a different manner.

In lesions of the cardiac area of the stomach, the cardiac orifice is almost always affected, and the patient comes for an examination because there is difficulty in deglutition. An examination reveals a stricture of the cardiac orifice together with a small or large filling defect in the immediate vicinity. The activity of the stomach itself is normal and, unless the lesion is very extensive, there is no interruption of the peristaltic waves.

In lesions in the body of the stomach, one may have an extensive growth, and yet the patient may complain of very few symptoms, inasmuch as the motor activity is not interfered with. As this lesion rarely affects the cardiac or the pyloric orifice, obstructive symptoms are absent, the stomach emptying at the normal rate or perhaps a little more rapidly than normally. The roentgen-ray examination of the stomach of this form generally shows that the peristaltic waves are interrupted in their course at the seat of the lesion, inasmuch as the lesion itself is hard and indurated, and does not admit of further peristaltic movements. In addition a persistent filling defect is almost always present. This filling defect is produced by the growth in the stomach wall bulging generally more or less into the lumen of the organ itself, so that it is outlined by the bismuth in the stomach proper and presents the appearance of an indentation. In the third class of cases, that is, in lesions about the pylorus, the symptoms arise early as a rule and are due to a partial obstruction which quickly attracts the patient's attention to the gastric disorder.

From a roentgenological point of view we classify growths at the pylorus into two forms.

The first, the annular carcinoma, has its origin within the pylorus itself, and, although it may be very small in size, produces symptoms relatively early, as it soon causes a greater or less degree of obstruction.

The second type also has its origin at the pylorus; it is not annular in form, but invasive, most frequently extending along the wall of the stomach, especially at the pylorus. Such a growth may, or may not, produce early obstruction.

The annular type of carcinoma is easily recognized, inasmuch as the stomach is observed to be perfectly normal except at the pyloric end. The pylorus, instead of being clear-cut and sharp, is generally somewhat thickened and slightly depressed in the center, so that the structure assumes the shape of a crater.

The second type of carcinoma may exist for some time without being recognized, because in the absence of any symptoms of obstruction the patient, being still in a comfortable state, does not present himself for an examination. In this type of growth one finds a persistent filling defect in or close to the pylorus, and ascending away from it. The mass is indurated and free from peristaltic waves, since the waves pass over the area and are lost.

In cases of partial obstruction the stomach begins to show a very definite change. In the early stages we find active contractions of the organ with a slow elimination of its contents. Another very significant sign is that a portion of the stomach just within the pylorus and on the greater curvature in the pyloric region shows a tendency to bulge. The cause of this condition is as follows: The active contractions of the stomach force all of the food toward the pyloric region; the pylorus not being patent, as a result of this constant pressure the prepyloric region becomes dilated, so that the plate presents the pylorus, apparently not at the end of the stomach, but with the prepyloric region extending further to the right than the pylorus, the latter resting on the top of the stomach and pointing to the splenic region. This prepyloric bulging is dependent

largely upon the duration of the affection. In the early stages it is very small, but, as the condition advances, it may reach the size of a hen's egg. As the condition advances still further, dilatation begins to take place, and after a time practically the entire fundus yields, so that a typical sacular formation is produced and all the bismuth rests in the fundus. When the stomach is in this condition, an X-ray examination will show a retention of contents for from 10 to 20 hours.

Unless due care be exercised, one may easily be misled by certain reflex or spastic conditions of the stomach. It is not uncommon to observe a stomach presenting a persistent filling defect in a definite area continuing over a period of an hour or two, and in a single instance under our observation for 48 hours, due to this condition. In doubtful cases the question of spasm of the stomach can easily be eliminated by the administration of full doses of atropin for one or two days, until the patient is well under its influence. A second examination, made under these conditions, will immediately show that the suspicious area has completely vanished, and that the condition previously observed was due to spasm.

In the X-ray study of gastric carcinoma the differential diagnosis between this condition and ulcer is often very difficult. It is still a much debated question as to whether carcinoma of the stomach has its origin primarily as such, or is the result of a transition from an old ulcer. If the latter view be correct, one can readily understand the difficulty in determining when the benign condition begins the transition into malignancy. The situation of both carcinoma and ulcer is very frequently the same, although we observe carcinoma more frequently on the greater curvature than ulcer.

In the differential diagnosis between the two conditions the points to be taken into consideration are as follows:

1. *Peristalsis.*—In carcinoma, unless there is obstruction, there is always hypermotility with rapid evacuation of contents. In ulcer there is always hypermotility, with a spasm of the pylorus and more or less retention of contents.

2. *Position.*—Carcinoma may occur in any part of the stomach. The invasive lesions are more frequently seen on the lesser curvature near the pylorus, and less frequently on the greater curvature. The massive growths are more generally seen on the greater curvature, whereas ulcer is generally observed on the lesser curvature near the pylorus, although it may occur on the greater curvature.

3. *Filling Defect.*—In carcinoma the filling defect is generally surrounded by an invasive area, which, while not appearing on the plate, interferes with motility, producing an apparently large dead area. In ulcer the filling defect is much smaller, and is not so apt to have the immediate peristaltic waves interfered with, although, if the inflammatory area be large, there may be also a dead area surrounding the filling defect.

Carcinoma of the pylorus in the earliest stage is generally annular and produces a crater-like appearance. In ulcer of the pylorus there is a filling defect, but it does not generally assume the crater-like appearance.

When any of these conditions pass on to the obstructive stage, the change that is caused by the dilatation may mask the signs associated with the filling defect.

In our experience, in the very early stages of gastric cancer, it is frequently impossible to determine whether we are dealing with a malignant or a simple ulceration. Our main aim, however, is to decide whether the lesion at hand is really an ulcer, or not. Inasmuch as indurated gastric ulcers have at times a tendency to become malignant and produce roentgenograms similar to those which are cancerous, they must be included in the same class. The exact diagnosis must be cleared up by further investigation into the clinical history and the examination. But even under these conditions there are many instances in which the diagnosis may still remain in doubt until operation, and microscopic examination of the specimen after removal, finally establish the true nature of the disease.

In the later stages of gastric cancer, however, when the growth is large, it is usually a very simple matter to arrive at a correct conclusion regarding its malignancy, but at this stage the symptoms are usually so well established that it is hardly necessary to seek further evidence by means of roentgen-ray examinations.

The X-ray, however, even at this stage, furnishes us important evidence as to whether the tumor is or is not operable, inasmuch as it clearly establishes the location and extent of the growth, together with the degree of obstruction. Hence, in many instances, it will indicate the usefulness or uselessness of surgical procedures.

Since we have taken up the positive phase of gastric cancer, it is well to draw some conclusion regarding the negative findings. If the fact can be established that there is an absence of all morphological defects in the wall of the stomach; that the peristalsis of this organ is normal, and that there is no tendency to even a partial obstruction, carcinoma of the stomach can usually be ruled out. This is an exceedingly important procedure, as a negative finding is of quite as much importance as a positive one.

In our roentgen-ray study of gastric cancer we have selected 50 consecutive cases, including those only concerning which we could feel confident of the correctness of the diagnosis. Of these, the growth was located in 34 instances about the pylorus; in nine it involved the body of the stomach without interfering with the orifices, and in seven the cardia was involved. It is interesting to note the relative incidence of the other signs of the disease in these special cases at the time when the X-ray examinations were made.

Of the 50 cases, the gastric secretion was obtained in 46. There was a normal acidity in four instances; a hypochlorhydria or an absence of acid in 36 instances, and a hyperchlorhydria in six instances.

In the 36 cases showing a hypochlorhydria, lactic acid was present in 28 instances, and the Oppler Boas bacillus in 24. Occult blood was present in the stools in 42 of all the cases.

A palpable tumor was observed in 34; dysphagia in seven; pain was present in 49; vomiting in 44; gastric hemorrhage

in 14; melena in eight; occult blood in 46; dilatation of the stomach in 24 cases.

Of these cases the X-ray gave positive evidence of disease in 46 instances, of which four were early cases and 42 were late cases. In two of the four early cases the roentgenogram gave a positive diagnosis of carcinoma. In the other two, however, an ulcerative lesion was found which was thought to be benign. The X-ray evidence, then, was positive in 42 of the late cases. It was positive, as far as the lesion was concerned, in all of the cases, but positive in only 95 per cent of the cases as regards the actual diagnosis of carcinoma. In the early cases the X-ray showed a lesion in all; in two of them, however, it was thought to be benign, but exploration proved the condition malignant.

This method of examination, according to our experience, possesses about the same diagnostic value as any of the other early signs of this disease, when taken alone, but in conjunction with the clinical evidence a positive diagnosis can almost always be made.

Inasmuch as the X-ray clearly reveals the evidence of an indurated ulcer in most instances, and in view of the fact that indurated ulcers are at times the beginning of cancerous growths, it affords a means of establishing early the diagnosis of gastric cancer.

From our studies of the many cases of cancer of the stomach, in which X-ray examinations have been made, we believe that we are justified in drawing the following conclusions.

1. The roentgen-ray offers most valuable assistance as an aid in the diagnosis of gastric carcinoma; and this is especially true when the lesion is situated in the so-called silent area. It should not be relied upon alone in the diagnosis of early cases without a strict consideration of the clinical aspect of the disease, but, when taken in conjunction with the other signs, it is of the greatest diagnostic value.

2. Indurated gastric ulcers give roentgenograms similar to those of carcinoma; but inasmuch as ulcers are frequently pre-

cursors of cancer, they may be grouped for practical purposes in the same class. It is often possible to determine their true nature only by microscopic examination of the excised area.

3. In the diagnosis of carcinoma of the stomach two conditions must be taken into consideration; first, the peristaltic waves of the stomach; and second, the morphological defect in the stomach.

4. In carcinoma of the cardiac area of the stomach there is usually a filling defect present, the activity of the stomach itself being normal, and, unless the lesion be very extensive, there is no interruption in the peristaltic waves. In lesions of the body of the stomach, the peristaltic waves are interrupted in their course at the seat of the lesion, because the lesion itself is hard and indurated, and does not admit of further peristaltic movements. There is also present a persistent filling defect. In pyloric carcinoma there are usually signs of early obstruction in addition to a filling defect of small or large size, according to the extent of the growth.

5. In carcinoma, unless there be obstruction, there is always hypermotility with rapid evacuation of contents. In ulcer there is hypermotility with pylorospasm, and more or less retention of contents. In carcinoma the filling defect is generally surrounded by an invasive area, interfering with the motility, and producing a large dead area, whereas in ulcer the filling defect is much smaller, and is not so apt to interfere with the immediate peristaltic waves.

6. The roentgen-ray furnishes us with important evidence regarding the operability or non-operability of the growth, pointing out, as it does, the location and extent of the growth, together with the degree of obstruction and the amount of involvement.

7. Negative findings are at times quite as important as positive ones, inasmuch as absence of the various X-ray signs of cancer affords presumptive evidence of the absence of this affection.

A REPORT OF SEVENTY CASES OF BRAIN TUMOR.*

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It is but necessary to review the surgical literature of the past two years¹ to appreciate not only the advance that has been made in the localization and treatment of intracranial new growths, but also the number of problems in this field that require elucidation. Many of these are still fundamental problems. The necessity of early diagnosis and early operative treatment, though often urged, requires further emphasis; for 10 per cent of the patients that come into surgical hands are blind on admission. The average mortality in the practice of

those most interested in the surgery of brain tumors is over 30 per cent (excluding Cushing's 8 to 10 per cent), apparently to a large extent because the question of the control of hemorrhage has not been altogether solved. Infection, especially in the nasal approach to hypophyseal tumors, has been a factor of importance in operative results (a recent report recording 14 deaths from meningitis); and in view of this danger it would seem wise to substitute, when possible, an aseptic approach to the chiasmal region for the present popular nasal route. Whether or not the removal of the infiltrating type of glioma should be attempted, what is the site of election for decompressive defects, whether one-stage or two-stage operations should be employed, even the choice and method of anesthesia, are questions more or less settled no doubt in the minds of

* The study of these cases was begun over a year ago, but the publication of the report was delayed. It was thought best to publish the report as it stands rather than include the total number of cases which have come under observation to the present time—a total of over 100.

TABLE I.—CEREBRAL AND BRAIN-STEM TUMORS CERTIFIED BY OPERATION OR AUTOPSY.

	Surg. No.	Type of tumor.	Location of tumor.	Operation.	Lesion verified at	Result.
1	31937	Tuberculoma.....	Subcortical, Pre-Rolandic..	Enucleation.....	Operation..	Improved.
2	32813	Cystic glioma.....	Subcortical, Pre-Rolandic..	Enucleation, total (?).....	Operation..	Well.
3	33767	Cystic glioma.....	Subcortical, Int. Capsule..	Enucleation.....	Operation..	Improved.
4	33206	Cyst, recurrent.....	Subcortical, Pre-Rolandic..	Enucleation.....	Operation..	Unimproved.*
5	32307	Glioma.....	Optic thalamus, right.....	Subtemporal decompression...	Autopsy...	Returned to work for five months. Died suddenly.
	32913					Improved.*
6	32368	Glioma.....	Diffuse, paracentral region.	1. Subtemporal decompression..	Operation..	Improved.*
	33372			2. Partial removal.		
7	30873	Glioma.....	Third ventricle.....	Cerebellar exploration.....	Autopsy...	Dead three days after operation.
8	31135	Glioma.....	Third ventricle.....	Sellar decompression.....	Operation..	Unimproved.*
9	31801	Tuberculoma.....	Midbrain (solitary).....	None.....	Autopsy...	Dead.
10	34145	Cystic glioma.....	Temporal lobe.....	None.....	Previous Operation.	Improved.
11	34023	Pachymeningitis interna hemorrhagica.	Right hemisphere.....	Exploratory craniotomy. Removal of membrane.	Operation..	Improved.
12	34404	Glioma.....	Left frontal lobe.....	Exploration and decompression.	Operation..	Unimproved.
13	34645	Glioma.....	Left temporal lobe.....	1. Decompression.	Operation..	Improved.
	35033			2. Exploratory craniotomy.		
14	32720	Glioma.....	Right temporal lobe.....	1. Decompression.	Operation..	Improved.
	35005			2. Partial removal of tumor.		
15	30903	Glioma, calcified.....	Right hemisphere.....	None.....	X-ray.....	Not treated.
16	34515	Cyst.....	Hypophysis.....	Craniotomy. Evacuation of cyst.	Operation..	Well.
17	35166	Glioma (?). Healed abscess (?).	Right temporal lobe.....	Exploratory craniotomy.....	Operation..	Improved.
18	34053	Cyst.....	Third ventricle.....	Craniotomy. Evacuation.....	Operation..	Well.
19	33974	Encephalitis.....	Right hemisphere.....	Excision of mass.....	Operation..	Well.
20	35586†	Glioma.....	Left temporal lobe.....	Exploration and decompression.	Operation..	Improved.
21	31628	Aneurism of internal carotid, bilateral.	Temporal fossae.....	1. Decompression.	Autopsy...	Returned to work for 16 months. Then sudden death.
	32976			2. Repair of hernia cerebri.		
22	34398	Glioma.....	Left temporal region.....	Exploration. Excision of tumor.	Operation..	Well.
23	34722	Glioma.....	Left frontal lobe.....	Exploration and decompression.	Autopsy...	Dead.
24	35534	Endothelioma.....	Left frontal lobe.....	Enucleation (3 stages).....	Operation..	Improved.
25	35658	Glioma.....	Right frontal lobe.....	Exploratory craniotomy. Extirpation.	Operation..	Improved.
26	36118	Cyst (arachnoidal).....	Right temporal lobe.....	Craniotomy. Evacuation of cyst.	Operation..	Well.
27	35746	Glioma (?). Neuroma (?).	Right paracentral region.....	Craniotomy. Excision of tumor.	Operation..	Well.
28	35580	Cyst (arachnoidal).....	Right temporal lobe.....	Exploration. Evacuation of cyst.	Operation..	Improved.
29	34026	Glioma.....	Third ventricle.....	1. Decompression.	Operation..	Unimproved.
				2. Exploratory craniotomy.		
30	25006	Endotheliomata, recurrent (?).	Right parietal region.....	Craniotomy. Enucleation.....	Operation..	Well.
	36746					

* The patient has since died.

SUMMARY OF TABLE I.

Number of cases operated upon.	Number of operations.	Operative mortality.	Case mortality.	Apparently well on discharge.	Improved.	Unimproved.
27	32*	6.2%	7.4%	8	13	4

* Surg. No. 35534, in which three stages were necessary for the removal of the tumor, is counted as one operation.

TABLE II.—CEREBELLAR AND CEREBELLOPONTINE TUMORS CERTIFIED BY OPERATION OR AUTOPSY.

	Surg. No.	Type of tumor.	Location of tumor.	Operation.	Lesion verified at	Result.
1	33874	Cyst.....	Intracerebellar.....	Suboccipital exploration. Evacuation.	Operation..	Well.
2	32311	Endothelioma.....	Cerebellopontine angle.....	Enucleation.....	Operation..	Dead five days after operation.
3	31325	Glioma.....	Cerebellum and pons.....	Exploration.....	Autopsy...	Dead three hours after operation.
4	30801	Cyst.....	Intracerebellar.....	Evacuation.....	Operation..	Well.
5	30724	Cyst.....	Intracerebellar.....	Evacuation.....	Operation..	Well.
6	30854	Glioma.....	Vermis, cerebellum.....	Partial removal.....	Operation..	Improved.*
7	31639	Endothelioma.....	Cerebellopontine angle.....	None.....	Previous operation.	Improved.
8	32775	Ependymitis. Internal hydrocephalus.	Fourth ventricle.....	1. Subtemporal decompression.	Autopsy...	Unimproved.†
				2. Cerebellar exploration.		
9	35309	Cyst.....	Cerebellum.....	1. Exploration and decompression.	Operation..	Well.
	35731			2. Evacuation.		
10	35519	Cyst.....	Intracerebellar.....	Excision.....	Operation..	Well.
11	34445	Cyst (arachnoidal).....	Over cerebellum.....	Evacuation.....	Operation..	Well.
12	36092	Cystic glioma.....	Cerebellum.....	Excision.....	Operation..	Well.

* Dead four months after operation. † Died some time after operation.

SUMMARY OF TABLE II.

Number of cases operated upon.	Number of operations.	Operative mortality.	Case mortality.	Apparently well on discharge.	Improved.	Unimproved.
11	13	15.4%	18%	6	2	1

TABLE III.—PRESUMED CEREBRAL TUMORS; NOT CERTIFIED.

Surg. No.	Presumed location of lesion.	Operation.	Result.
1 32713	Left cerebral hemisphere.....	Exploratory craniotomy.....	Unimproved.
2 31874	Unlocalizable.....	Right subtemporal decompression.....	Improved.
3 31786	Hemisphere, left.....	Exploration and decompression.....	Unimproved.
4 30791	Unlocalizable.....	Right subtemporal decompression.....	Improved.
5 31822	Unlocalizable (metastatic?).....	Right subtemporal decompression.....	Improved.
6 32917	Unlocalizable.....	Right subtemporal decompression.....	Improved.
7 33200	Hemisphere, left.....	Exploratory craniotomy.....	Unimproved.
8 33359	Unlocalizable.....	Right subtemporal decompression.....	Improved.
9 33480	Hemisphere, left.....	1. Exploration and decompression. 2. Transcortical exploration.	Unimproved.
10 33815	Frontal lobe, left.....	Exploration and decompression.....	Improved.
11 31406	Hemisphere, left.....	None.....	Not treated.
12 34701	Hemisphere, left.....	Exploratory craniotomy.....	Improved.
13 35364	Hemisphere, left.....	1. Exploration and decompression. 2. Exploration.	Improved.
14 34849	Hypophysis (?), internal hydrocephalus.....	Ventricular puncture.....	Unimproved.
15 33012	Third ventricle.....	Cerebellar exploration.....	Improved.
16 36048	Unlocalizable.....	Exploration and decompression.....	Improved.

SUMMARY OF TABLE III.

Number of cases operated upon.	Number of operations.	Operative mortality.	Case mortality.	Apparently well on discharge.	Improved.	Unimproved.
15	17	0	0	0	10	5

TABLE IV.—PRESUMED CEREBELLAR AND CEREBELLOPONTINE TUMORS NOT CERTIFIED.

Surg. No.	Presumed location of lesion.	Operation.	Result.
1 35905	Cerebellum.....	Suboccipital exploration.....	Improved.
2 33837	Cerebellum.....	Suboccipital exploration.....	Unimproved.
3 33683	Cerebellopontine angle.....	Suboccipital exploration.....	Dead. In coma when operated upon.
4 32049	Cerebellum (metastatic?).....	None.....	Dead. Died suddenly before operation.
5 30887	Cerebellum.....	Suboccipital exploration.....	Unimproved.
6 30999	Cerebellum.....	Suboccipital exploration.....	Improved.
7 31636	Cerebellum.....	Suboccipital exploration.....	Improved.
8 32022	Cerebellum.....	Suboccipital exploration.....	Dead, 24 hours after operation.
9 32523	Cerebellum.....	Suboccipital exploration.....	Unimproved.
10 32854	Cerebellum.....	Suboccipital exploration.....	Improved.
11 32169	Cerebellum.....	None.....	Not treated.
12 31701	Pons.....	None.....	Not treated.

SUMMARY OF TABLE IV.

Number of cases operated upon.	Number of operations.	Operative mortality.	Case mortality.	Apparently well on discharge.	Improved.	Unimproved.
9	9	22%	22%	0	4	3

individual surgeons, but as questions influencing the mortality, and the results of surgical procedures in general, still open to discussion.

We have reviewed the cases of brain tumor in patients who have entered the surgical service of Dr. Halsted between September 1, 1912, and January 1, 1915; and in the present communication we wish to consider them for the purpose of commenting upon some of the problems indicated. We wish further to indicate the value in our hands of some of the more common diagnostic aids, to relate a few experiences in the pathology and differential diagnosis of brain tumors, and, finally, to emphasize steps in surgical technic that have favorably influenced our mortality and operative results.

In the 70 cases which form the basis of this report are included conditions other than true brain tumor, *i. e.*, ependymitis, pachymeningitis interna hemorrhagica, encephalitis, arachnoiditis, cerebral tubercle, dural gumma, and aneurism

of the internal carotid artery. Yet the symptoms in these conditions simulated so closely those of brain tumor that operations were usually performed under the supposition that a new growth was present. Of these 70 cases, the nature and position of the lesion has been established by us at operation or at autopsy in 40, or 57 per cent; and two additional cases were certified through operations performed by Cushing. The remaining 28 patients presented definite signs and symptoms of brain tumor and in the great majority of instances were operated upon, the operation, however, failing to disclose the lesion. These cases may be grouped as shown in Tables I, II, III and IV.

Of the 70 patients, 62 were operated upon. Of the eight patients not operated upon, six refused operation, one had such extensive pulmonary tuberculosis that operation seemed inadvisable, and one died suddenly in the ward before operation. Seventy-one major operations were performed upon

these 62 patients, *i. e.*, upon several patients, on a second admission, an exploratory craniotomy was performed subsequently to a subtemporal decompression. There were six deaths occurring between 24 hours and five days after operation—an operative mortality of 8.6 per cent; a case mortality of 9.6 per cent. Two patients subsequently died in the hospital, their condition and subsequent death being apparently uninfluenced by our operative procedures. Including these the total mortality is 11 per cent and 12.8 per cent, respectively. There were no deaths upon the operating table. The mortality list, as shown in the accompanying analysis, includes a moribund patient operated upon as an emergency in the last stages of cerebral compression.

1. Surg. No. 33683. Comatose for three days before admission to the hospital. Operation performed as an emergency with the patient in the last stages of cerebral compression. The patient stood the operation remarkably well, but failed to respond, and died 24 hours later. No autopsy.

2. Surg. No. 32022. Operated upon for supposed cerebellar tumor. Lesion not found at operation. There was a considerable amount of difficulty with the anesthesia (cyanosis), but his condition was good at the end of the operation. It remained good during the night, but on the following morning he suddenly became cyanotic, his temperature rose to 103.5° F., his pulse to 170-180. He was given oxygen and improved remarkably; his pulse and temperature dropped, and his cyanosis entirely disappeared. Twenty-six hours after operation he had a second similar attack, and died. No autopsy.

3. Surg. No. 30873. Operated upon for supposed cerebellar tumor. Unusually bloody operation, due to the enormous venous sinuses in the occipital bone. In opening the dura an anomalous venous sinus was cut, with a resulting hemorrhage which was controlled with difficulty. Lesion not found at operation. For 20 hours after operation the patient's condition was good. At the end of that time he was seized with numerous convulsions (cerebellar fits), characterized by opisthotonos, extension and internal rotation of the arms, and extension of the legs, with plantar flexion of the feet; Cheyne-Stokes respiration; stupor. On the possibility that perhaps a hemorrhage had occurred from the damaged sinus, the wound was opened, but found to be perfectly dry. Death 24 hours after operation. Autopsy. Tumor about the third ventricle. No hemorrhage.

4. Surg. No. 32311. Operated on for right cerebello-pontine tumor. Tumor the size of a walnut found in angle. It was enucleated and the bleeding readily controlled. The tumor, which proved to be a dural endothelioma, was quite adherent to the skull and total extirpation was impossible. Recovery from operation, with difficulty of respiration and speech. Several spells of asphyxia resulted, and the patient died five days later. No autopsy.

5. Surg. No. 31325. Cerebellar exploration for a presumed cerebello-pontine tumor. The tumor could not be located at operation, although a good exploration of both cerebello-pontine angles was possible. The operation was uneventful except for a persistent cyanosis. The cyanosis was not lessened by intratracheal insufflation, change of position, or stimulants, and the patient died three hours after the operation. At autopsy, a large infiltrating glioma was found in the medulla and the left lobe of the cerebellum. An enlarged thymus, which constricted the left innominate vein, was undoubtedly responsible for the cyanosis during operation.

6. Surg. No. 34722. Left exploratory craniotomy for a tumor presumably involving the left temporal lobe. Operation uneventful. The tumor was not disclosed, and the operation resulted in

a decompression. A ventricular puncture was done, but no cerebrospinal fluid was obtained. A drop or two of blood escaped from the needle. For 48 hours after the operation the condition was good. Then there was a sudden rise in temperature to 106° F., great restlessness, numerous convulsions, and death in four hours. Autopsy. A large subcortical glioma was found, extending into the left lateral ventricle. Both ventricles were full of blood, presumably from the puncture of the tumor by the ventricle needle.

In 33 cases the lesion was disclosed at operation, *i. e.*, in 53 per cent of the cases operated upon. The operative treatment consisted in the attempt to remove the lesion completely in 28 cases; in seven of these we accomplished no more than a partial extirpation. In four cases the size or situation (in the speech area, etc.) of the growth made an attempt at removal unwise. In one case the operation consisted in the partial removal of the dura and hemorrhagic membrane. Thirty-eight operations were performed upon these 33 patients. There was one death, an operative mortality of 2.6 per cent, a case mortality of 3 per cent.

Upon the remaining 29 patients a simple decompression, or an exploratory craniotomy combined with a decompression, was done in 21 instances; a cerebellar exploration and decompression in 13 instances. (In five cases, two cranioplastic operations, or both an exploratory craniotomy and a cerebellar exploration, were done.) The operative mortality in this group of cases was five, or 14 per cent; the case mortality, 17 per cent.

Sufficient data are not yet at hand to enable us to state at present the late results of our operative procedures in these 70 cases; and the determination of the point must be left for a subsequent report. The immediate results may be summarized as follows:

Fifteen patients left the hospital apparently well; 29 were greatly improved, with the relief of all pressure symptoms; 11 remained unimproved. Six patients died within from 24 hours to five days after operation; two patients eventually died in the hospital.

Pathology.—As previously noted, the character and site of the lesions are known in 42 of the 70 cases forming the basis of this report. In 30 cases the lesion involved the cerebral hemispheres, mid-brain and hypophysis; in 12, the cerebellum or paracerebellar regions. The following table indicates the character and location of the lesion:

Type of lesion.	Cerebral hemispheres.	Mid-brain.	Hypophysis.	Infracerebellar.	Extracerebellar (cerebellopontine, cerebellopharyngeal, etc.)
Glioma	14	3	3		
Cyst	3	1	5	1	
Endothelioma	2				2
Tuberculoma	1	1			
Syphiloma	1				
Encephalitis	1				
Ependymitis					1
Pachymeningitis interna hemorrhagica	1				
Aneurism, internal carotid artery	1				

The table shows the large percentage of glioma as compared with other varieties of lesion and the infrequency of the infectious granuloma, tuberculoma and syphiloma.

Gliomata.—Gliomata formed 50 per cent of the total number of lesions in this series. Of the cerebral gliomata, six were cortical, 11 were entirely subcortical. Eleven were diffuse, without a definite line of demarcation from the surrounding cortex; six were more or less circumscribed, in the sense that they allowed of a satisfactory enucleation. Twelve were solid tumors; five had undergone a more or less extensive cystic degeneration.* Of the cerebellar gliomata, two were cortical, one subcortical; two circumscribed, one diffuse; two solid, one cystic.

In all cases the gliomata were comparatively large. In consistency they varied from relatively hard to extremely soft gelatinous growths resembling a colloid carcinoma. In most instances the histological picture was that of a typical glioma; in several cases the closely packed round cells presented the picture of, and could not certainly be differentiated from, a round-celled sarcoma.

Cysts.—Of the 11 cysts which occurred in this series, seven belong to the group of simple serous cysts, one arose from an embryonal *Anlage* (Rathke's pouch?), and three are arachnoidal cysts. Five of the seven simple cysts occurred in the cerebellum, which appears to be their seat of predilection. They presented the typical characteristics—a thin, gelatinous wall easily separated from the surrounding apparently normal brain tissue, and a yellowish or slightly brownish fluid which, rich in fibrin, rapidly clotted on exposure to the air. The origin of these so-called simple cysts is not yet clearly understood. Although it may be difficult conclusively to demonstrate this association, they appear to be derived from solid tumors (gliomata and sarcomata) by a process of degeneration. The occurrence of what are apparently cysts having the usual cyst wall and characteristic fluid, but which on careful study show a mass of tumor tissue of varying size in the wall of the cyst, lends support to this view. Councilman,² however, states that "the cysts are not the result of cell secretion nor do they represent areas formerly the site of degeneration. They are due to the fluid absorption of the tissue and represent an accentuation of a condition common to the entire tumor."

The cyst arising from an embryonal *Anlage* was about 2 cm. in diameter and lay in the region of the third ventricle. At operation (an intracranial hypophyseal approach) a clear fluid was evacuated, containing numerous shimmering cholesterol crystals. Unlike the usual cystic fluid, it did not clot on standing. The cyst wall (Fig. 1) consists of layers of stratified epithelium, the basal layer columnar and resting upon a sharply defined basement membrane. Above the layer of columnar cells are from 6 to 10 or more layers of flattened epithelium, becoming squamous at the surface. The origin of this cyst from Rathke's pouch seems probable.

* In the classification of cystic lesions, those in which there was a demonstrable fragment of gliomatous tissue are grouped under gliomata; those without demonstrable tumor tissue are grouped under "cysts."

The arachnoidal cysts, three of which occur in this series, form an interesting group of cases. Arising in the majority of instances as a consequence of infection (especially from the ear) or of trauma, they give rise to general pressure symptoms and focal signs simulating tumor. Two occurred over the cerebral hemispheres, one over the cerebellum. As seen at operation, two of the cases presented a local collection of cerebrospinal fluid enclosed by the thickened, opaque pia-arachnoid. In one of these cases the underlying cortex appeared normal; in the other there was a definite atrophy of the underlying convolutions. In the third case the condition was not definitely seen. The patient presented marked pressure symptoms plus nystagmus and staggering gait; and at operation the left cerebellar lobe herniated into the dural defect more markedly than the right. Exploration about the left lobe showed adhesions between the pia and the tentorium, during the separation of which there was a sudden discharge of cerebrospinal fluid. The exact location of this fluid was not determined, but apparently it lay between the cerebellar pia-arachnoid and the tentorium.

The arachnoidal cysts should not be confused with conditions in which, as a result of disturbed cerebrospinal circulation, fluid collects under tension in the various cisternæ. It has been our experience to explore the cerebellum in a case presenting indefinite symptoms, and to find the median cisternæ enormously distended with fluid, and the pia-arachnoid opaque and thickened—a picture, therefore, resembling that of an arachnoidal cyst. The subsequent post-mortem examination showed a large tumor involving the optic thalamus and internal capsule. It is, indeed, frequently observed in explorations for cerebellar lesions that the cisternæ are distended with fluid, and it is a common practice to open them in order to relieve tension. Local collections of fluid are also sometimes observed over tumors (as in those in the cerebellopontine angle).

Endotheliomata.—Of the four patients in this series one was not operated upon by us, but returned with definite signs of local recurrence about three years after a cerebellopontine-angle tumor had been removed by Cushing. Of the three other cases, one occurred in the cerebellopontine angle, two over the hemispheres. One of the latter is interesting, in that it was attached to and apparently arose from the falx cerebri, and for the most part was subcortical, reaching the surface over the lateral aspect of the frontal lobe. At the point where it presented on the surface it had provoked a hypertrophy of the overlying skull so that an X-ray diagnosis of osteoma of the skull had been made.

Although few in number, these cases serve to illustrate the most important surgical aspect of these tumors, i. e., that they may be multiple, and that, unless completely removed with a wide area of attached dura, they are prone to local recurrence. Two of the patients came to us with recurrent tumors; one of these cases, Surgical No. 25006, is an example of recurrent and multiple tumors. The patient, admitted with general pressure symptoms, focal epileptic attacks in the left hand and arm, and a mild grade of motor aphasia, had been operated upon in St. Louis in 1908, and a dural endothelioma lying over the

motor strip had been successfully removed. The aphasia apparently was not accounted for at that time. He entered The Johns Hopkins Hospital in November, 1909, with recurrent symptoms and with more pronounced aphasia. The third exploration was directed farther forward than the first or second. A recurrent tumor was found at the site of the previous operations, and a second tumor, about the size of a walnut, was discovered indenting and compressing the motor speech area. Between the two tumors lay a strip of apparently normal dura, 4 cm. in width. Whether this second tumor should be considered a distinct growth, or a regionary metastasis from a primary tumor, is not clear. Endotheliomata do not as a rule metastasize; and the intervening normal dura does not suggest a direct extension from a primary growth. The possibility of a second tumor arising by implantation from a primary growth should be thought of. That tumors may be multiple and entirely distinct is shown by the occasional occurrence of bilateral endotheliomata in the cerebellopontine angles.

We shall make but few comments upon the cases of tuberculoma, syphiloma, encephalitis and ependymitis that occur in this series. Of the tuberculoma, both were solitary tumors, one in a patient without symptoms or signs of tuberculosis elsewhere; one in a patient showing pulmonary tuberculosis. The cerebral tubercle, although completely broken down, possessed a thick wall (Fig. 2), so that its complete removal without rupture was comparatively easy. The syphiloma occurred in a patient whose only symptom was a persistent headache, confined to a small area over the left temporal region. At operation three small dural gummata, closely grouped together, were removed. The cases of encephalitis and ependymitis presented symptoms and signs characteristic of tumor; in the former the localized affected area was excised; in the latter, which subsequently came to autopsy, no lesion excepting a chronic basilar meningitis and ependymitis was found to account for the high grade of internal hydrocephalus which was present.

Pachymeningitis Interna Hemorrhagica.—The case is of interest from a clinical as well as a pathological standpoint, and therefore is described in some detail.

Surg. No. 34023. Pachymeningitis interna hemorrhagica. General pressure symptoms. Loss of memory, irritability, change in habits, mental dullness. Right exploratory craniotomy with the disclosure of an extensive hemorrhagic membrane. Recovery.

The patient, a male of 26, by occupation a farmer, was admitted to the hospital February 28, 1914, complaining of headache and loss of vision. His past history was unimportant. His present illness began in January, 1913, with headaches and occasional vomiting. There was no history of previous injury to the head; indeed, no etiological factor. The headache was generalized in "a heavy, dull, severe ache" present every morning, becoming less severe in the afternoon. His eyesight began to fail in March and continued to grow steadily worse until he was almost blind. In November, 1913, a decompression was done at another hospital, with relief of the headaches for a month and a half. Since that time they had become progressively worse. He had noticed loss of hearing for the three weeks previous to admission.

Examination.—The patient presented a large cerebral hernia, the result of the previous decompression. This was unusually tense. The positive neurological findings were a high grade of

choked disc in both eyes (5-6 diopters); blindness of the right eye, almost complete blindness of the left; convergence palsy of the right eye; marked impairment of hearing in both ears, about equal on the two sides; marked disturbance in memory; irritability and change of habits. The X-ray showed general convolitional atrophy and destruction of the posterior clinoid process. A probable diagnosis of tumor in the frontal region was made.

Operation.—March 4, 1914. A large bone flap was turned down in order to expose the frontal and paracentral regions. The dura mater was under enormous tension and bluish in color over the entire area exposed. From a small preliminary opening made in it, a blood-tinged fluid spurted a distance of six feet. After evacuation of a very large amount of this fluid, the dural tension rapidly diminished. When the dural flap was turned back, a remarkable picture presented. Underneath the dura was a false membrane extending over the entire hemisphere, red in color and in places a centimeter in thickness. Between this hemorrhagic membrane and the dura the fluid previously evacuated had collected. Friable festoon-like adhesions extended from the external surface of the membrane to the dura, the intervening space, therefore, having the appearance of a large multilocular cystic cavity containing blood-stained fluid and blood clots. After the evacuation of fluid and clots, it was evident that there was a continuous slow oozing of fresh blood into the cavity. Some of this fresh blood definitely came from the under surface of the dura, but that this was the only source of the bleeding could not be determined. On cutting through or separating the hemorrhagic membrane, we encountered a second thin and transparent membrane, beneath which was clear cerebrospinal fluid. This membrane suggested pia-arachnoid, but was of greater thickness. It could be lifted from the surface of the cortex, was readily separable from the hemorrhagic membrane, and, so far as could be determined, extended over the entire hemisphere. When this membrane was incised, the cortex was exposed. This also presented an unusual appearance: Along the sulci and blood vessels were yellowish lines and plaques suggesting an old healed infective process. Several of these plaques were excised, and on section proved to be made up of dense fibrous tissue. There was no evidence of a cerebral tumor. A portion of the dura and as much of the hemorrhagic membrane as possible were excised. The wound was then closed.

Post-Operative.—No post-operative complications. The hernia through the decompression defect collapsed after operation, but promptly became tense again. The patient was discharged from the hospital showing little, if any improvement.

Pathological Report.—Section of the tissue excised (Fig. 3) shows the dura considerably thickened and in places infiltrated with small round cells. In one place a large dural sinus appears to open directly into the hemorrhagic area. Intimately in contact with the dura (a condition not present at operation and due to fixation), but sharply demarcated from it, is the hemorrhagic layer. It consists almost entirely of red blood cells, with here and there an infiltration of small round cells and fibroblasts. The inner surface of this layer appears to have an epithelial covering. The second membrane is a distinct layer not to be confused with the epithelial covering of the hemorrhagic membrane. In structure it resembles dura.

Comments.—The condition is well known, although rare. The etiology is obscure. Virchow thought that the primary condition was a meningitis, the hemorrhage being secondary. Later observers, among others Trotter,² have believed that the hemorrhage is primary, often due to trauma, and that the bleeding arises from the rupture of veins crossing from cortex to dura. The condition is rarely, if ever, correctly diagnosed, owing to the variability in its symptomatology. Trotter has

recently reported a series of cases associated with trauma; it has been an unexpected finding in operations performed for epilepsy; it has been an unexpected post-mortem finding in individuals dying in institutions (Fig. 4).

Aneurism of the Internal Carotid Artery (Bilateral). *Surg. No. 31628.* Bilateral intracranial aneurism of the internal carotid arteries. Symptoms and signs of brain tumor. Calcified mass demonstrable by X-ray. Right subtemporal decompression. Complete relief of all pressure symptoms. Death 18 hours after operation. Autopsy.

The patient was a telegraph operator, 26 years of age. His symptoms began four years before admission with sudden violent frontal headache, nausea and vomiting. These symptoms persisted for six months, then gradually subsided. Loss of vision in the left eye began soon after the onset and progressed until this eye was completely blind. Disturbance of vision followed in the right eye and progressed very slowly. External strabismus of the left eye had been noticed for some time. Forgetfulness and mental dullness were evident.

Examination.—Positive findings: Suggestive parchment crepitus of skull over left temporal region. Left unilateral exophthalmos, but without pulsation. Optic atrophy in the left eye. Choked disc with swelling of 4 diopters and with hemorrhages and exudates in the right fundus. Complete blindness in the left eye; one-half normal vision with a contracted form field and a temporal hemianopsia for colors in the right. Paralysis of the left N. VI, and of the left N. V, both sensory and motor. Suggestive weakness of the right side of the face. Slight weakness of the grip in the right hand. Active reflexes, but equal on the two sides. The X-ray (Fig. 5) shows a series of shadows, consisting of broad, curved lines and plaques. Wassermann reaction negative.

Operation.—The patient, following the advice of his family physician, refused an extensive operation; therefore, only a right subtemporal decompression was done.

Post-Operative.—The choked disc in the right eye promptly subsided. The patient returned to his work and continued actively working for a year. He then gave up his position because of a reduction in his salary as a result of mistakes in the transmission of telegraphic messages. He felt perfectly well; was without headache, nausea, or other symptoms. Suddenly, 18 months after operation, he was aroused from sleep with terrific headache and vomiting, shortly became unconscious, and died within an hour.

Autopsy.—A view of the base of the brain (Fig. 6) shows a large aneurismal mass occupying the left temporal fossa and extending beyond the median line to the right. It was, at the time of removal of the brain, entirely covered by the dura and attached to the bone at the carotid canal. Upon the right side is a second smaller aneurism, 3.5 x 2 x 2 cm. in diameter, which has eroded the floor of the sella turcica. The hypophysis lies between the two masses, much compressed and flattened. The large mass, on being separated from the brain, shows clearly the internal carotid artery entering and leaving it at almost opposite poles. These vessels are about normal in size. The mass measures 24 cm. in circumference and 8 x 7 x 7 cm. in its various diameters. Its surface is smooth and roughly spherical, with the exception of three projecting knobs. On section, the wall of the aneurism varies from 1 cm. in thickness to paper thinness, and shows numerous areas of calcification. The sac is entirely filled with a dense laminated clot which can be lifted out *en masse*, and is entirely solid except for a narrow channel extending through the clot. The base of the brain, after removal of the mass (Photograph, Fig. 7), shows an almost complete destruction of the tip of the left temporal lobe. The mid-brain is compressed and dislocated to the right. The optic chiasm is rotated through an angle of 90°, so that it lies flattened against the mesial aspect of the right frontal

lobe. On section of the brain, the right ventricle is dilated, the left collapsed. The tip of the left temporal lobe has undergone an extensive cystic degeneration.

Examination of the skull after removal of the brain shows complete destruction of the posterior wall of the left orbit, destruction of the left anterior and both posterior clinoid processes, partial destruction of the right anterior clinoid process, and erosion of the floor of the sella turcica.

Comments.—The condition should have been correctly diagnosed; indeed, it was strongly suspected by Dr. Henry M. Thomas, who saw the patient with us. The sudden onset with terrific headache and vomiting, followed by a long interval (four years) without marked increase in the symptoms, indicated a vascular lesion; although a sudden hemorrhage into a vascular tumor might have given identical symptoms. The X-ray picture was striking; although we had never seen a similar picture, in retrospect, we should have considered that in no condition would concentric layers of calcification be so likely to occur as in a thick-walled, aneurismal sac. Although upon the left side the wall of the aneurism had eroded the orbit and lay against the fat behind the eye-ball, there was absolutely no pulsation of the globe, that is, no pulsating exophthalmos, and no bruit on auscultation over the skull. This may be explained by the rigidity of the walls of the aneurism due to the calcification and the almost complete filling of the sac with organized tissue. The cause of the sudden increased intracranial pressure leading to death was not determined; there was no rupture of either aneurism.

*Symptomatology and Diagnosis.**—It is not our purpose in the present paper to enter fully into the symptomatology and diagnosis in these cases, but rather to re-emphasize two of the possible causes of late interference in brain tumor cases and to indicate from our experience the value in our hands of some of the common aids in diagnosis.

One of the most important signs of an intracranial new growth is choked disc; and a subjective complaint of disturbance in vision may be a relatively early symptom. Yet, as has been repeatedly noted, even a high grade of choked disc is not incompatible with good vision; and perhaps this fact, more than any other, is responsible for the number of cases of blindness which occurs in every brain-tumor series.

Seven, or 10 per cent, of our patients were blind on admission, and in four others, vision was almost gone. There seems to be at present less confusion in the recognition and interpretation of choked disc; but how long surgical treatment may be safely delayed in the presence of this condition, is apparently as yet not clearly understood. It has been frequently urged that even in the absence of localizing signs, surgical measures should be contemplated as soon as a choked disc can be diagnosed; and we believe that the adoption of this teaching would in large measure prevent blindness. The time during which a choked disc may persist without causing permanent damage to vision is indeterminate; and when permanent injury to the nerve fibers has occurred, progressive loss of vision and even

* In the diagnosis of the cases included in this series we have had the assistance of Dr. H. M. Thomas, to whom we wish to express our indebtedness.

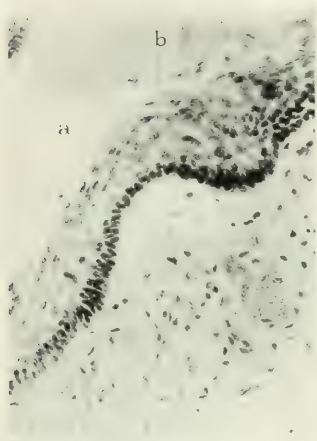


FIG. 1.—Cyst in the region of the third ventricle arising presumably from Rathke's pouch. *a*, Cyst cavity. *b*, Stratified epithelium forming the wall of the cyst.

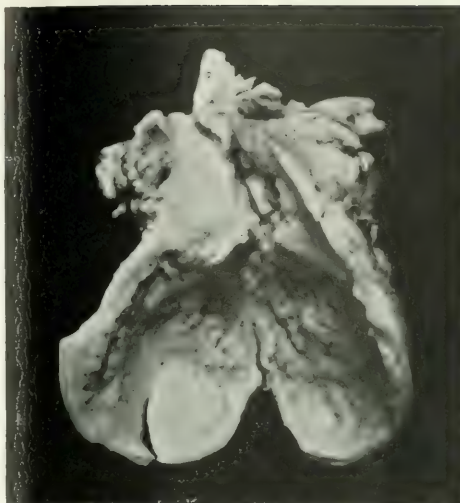


FIG. 2.—Broken-down cerebral tubercle, removed at operation unruptured, opened to show the thickness of the inflammatory wall.

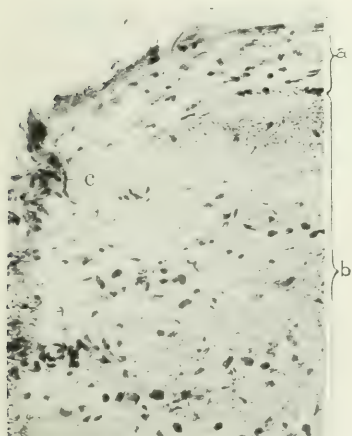


FIG. 3.—Section through hemorrhagic membrane. *a*, Dura mater. *b*, Hemorrhagic layer. *c*, Dural vessel apparently opening directly into hemorrhagic layer.

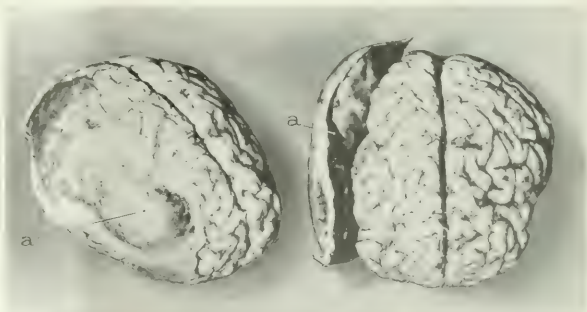


FIG. 4.—Case of unsuspected pachymeningitis interna hemorrhagica dying at Bay View Hospital. (Kindness of Dr. Boggs.) *a*, Dura over the hemorrhagic layer; in the photograph to the right the dura and hemorrhagic layer are reflected from the brain.

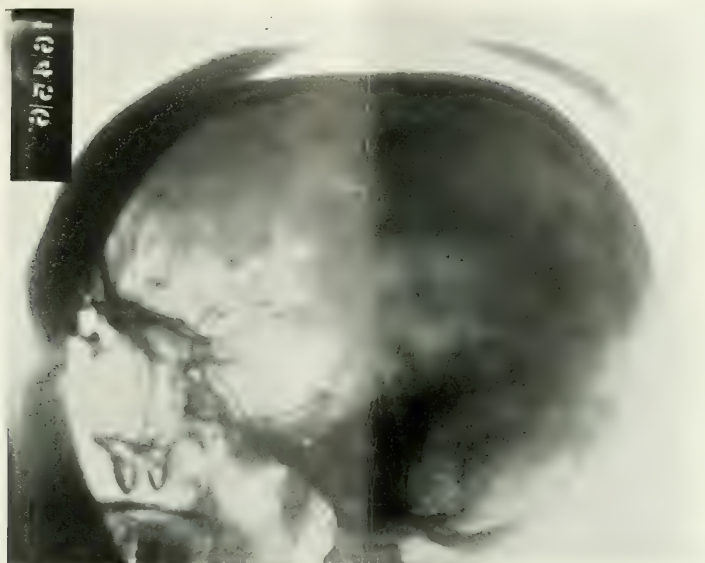


FIG. 5.—X-ray plate of a case of bilateral aneurism of the internal carotid artery. The areas of calcification in the aneurismal wall are seen as a series of broad, curved lines.

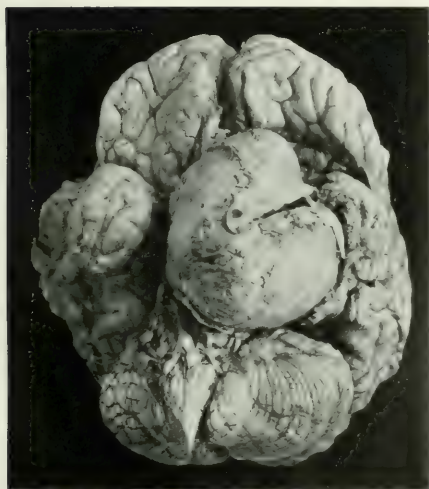


FIG. 6.—Case of bilateral aneurism of the internal carotid arteries. The smaller aneurism upon the right side is covered by the larger mass.

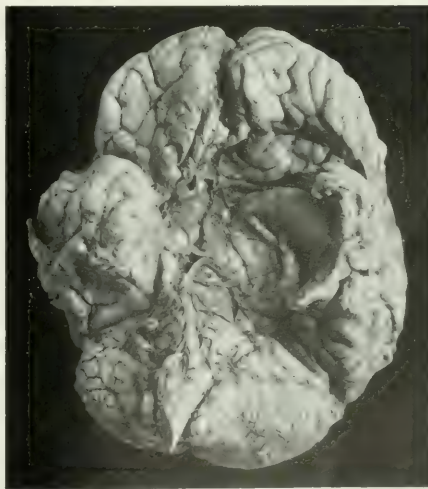


FIG. 7.—Case of bilateral aneurism of the internal carotid arteries. Aneurisms removed to show the compression and destruction of the top of the left temporal lobe.

blindness may supervene in spite of an adequate decompression with total subsidence of the choked disc. The demonstration of a normal visual acuity, as tested in the usual way, should not be taken as an indication of the absence of visual disturbance. It is only by careful perimetric examinations that early disturbances in vision can be demonstrated. Contractions in the color fields occur before alterations in the fields for form; and both may occur long before visual acuity, as ordinarily tested, is demonstrably affected.

The assumption, still too prevalent, that intracranial lesions are commonly of syphilitic origin, is another cause of delay in bringing cases into surgical hands. The occurrence of cerebral syphilomata is, in our experience, relatively uncommon as compared with that of true tumors. A single case of dural gumma occurred in the 40 cases certified by operation or autopsy. The Wassermann test was made in 53 cases. In three cases it was positive; in 50 negative. In one case in which a positive Wassermann reaction was obtained, the lesion proved to be a gumma; in one case, a glioma; and in one, the nature is not certified. The absence of a positive Wassermann reaction, with one exception, in a series of 28 certified cases of true tumor, argues well for the value of this test in excludingluetice lesions; and, although a negative Wassermann test does not positively rule out syphilis, yet it would appear unwise, especially in the presence of failing vision, to adopt antiluetic treatment, as is still commonly done, in the hope that the lesion may be luetic. As a case of glioma and a recent case of dural endothelioma show, syphilis and true brain tumor may coexist; hence a positive Wassermann is no certain indication of a cerebral luetic lesion. Our attitude toward the Wassermann reaction in intracranial conditions with choked disc and demonstrable impairment of vision is the attitude of surgeons toward lesions of the tongue in which a differential diagnosis between syphilis and carcinoma is in question—to use it as a guide for post-operative treatment.*

The X-ray as an aid in diagnosis in intracranial conditions still finds its greatest field of usefulness in the diagnosis of hypophyseal lesions; not only in their localization, but, from the associated deformities of the sella turcica, in the determination of their size, direction of growth, and, occasionally, of their character. Aside from hypophyseal tumors, however, the study of the X-ray plates in this series has proved of great aid in the diagnosis of intracranial new growths; for, while tumors producing a definite shadow are unfortunately uncommon, changes in the skull, such as erosion or thickening, vascular changes or changes more or less characteristic of internal hydrocephalus, are not infrequent. The value of the various phases of X-ray changes in intracranial lesions is considered in a paper which will shortly appear.

In this series the Bärány test has not been used frequently enough for us to make any positive statements as to its value in the diagnosis of subtentorial lesions. In two cases in which a cerebellar lesion was found at operation, the test was positive;

in two other cases in which the lesion was found, the test was suggestive but not outspokenly positive. In two cases of supposed cerebellar tumor in which the lesion was not found at operation, the test was negative. In two cases in which a careful search of both cerebellar lobes and cerebellopontine angles did not reveal a lesion, the test was absolutely positive. In one case of mid-brain tumor, the test was negative. In these few cases, then, the test has been helpful as corroborative evidence in cases with outspoken clinical signs; in cases in which the diagnosis has been uncertain, it has not been of great aid.

The demonstration of an *internal hydrocephalus* is of considerable value in cases in which a differential diagnosis between supra- and subtentorial lesions is uncertain. As is well known, tumors in either hemisphere rarely produce an internal hydrocephalus, whereas obstruction to the outflow of cerebrospinal fluid is a common accompaniment of tumors about the third ventricle, those compressing the aqueduct and those of the cerebellum. In cases in which the symptomatology and clinical signs leave us in doubt as to whether the lesion is anterior or posterior, the demonstration of an internal hydrocephalus may alone determine the site of operation. As has been noted, X-ray plates are of help in diagnosing internal hydrocephalus; more certain information, however, is obtained from ventricular puncture. This is a comparatively simple procedure, and may be done as a preliminary operation under local anesthesia, with or without the injection of 'phthalein; or at the same time as, and as a part of, the major procedure. The scalp flap turned down over either hemisphere need be only large enough to admit a small burr; and the single precaution necessary is to open the dura sufficiently to see that a cortical vessel is not injured by the introduction of the blunt needle. No untoward result has as yet followed the use of this procedure, but that there is a possibility of danger is shown by a death which has recently occurred following an exploratory puncture in the hope of discovering a cyst. The autopsy showed a hemorrhage into the ventricle following the introduction of the needle into a vascular tumor.

The use of phenolsulphonaphthalein to demonstrate an obstruction to the outflow of cerebrospinal fluid, as described by Dandy and Blackfan* for cases of hydrocephalus in children, has been employed in only three cases. Yet in each instance the results of the tests were quite striking, showing a complete block to the outflow of cerebrospinal fluid. In one case an intracerebellar cyst was found at operation; in two cases the position of the lesion has not been certified. It would seem that this test might be of considerable value in the diagnosis of intracranial conditions giving rise to a tumor symptom-complex, possibly in the differential diagnosis between cases of true tumor and those of internal hydrocephalus the result of ependymitis, etc., the latter sometimes giving rise to all the pressure phenomena common to tumors, but at autopsy showing no intracranial new growth.

Operative Technic.—In the surgical treatment of intracranial conditions, the approach to lesions and the safe closure of wounds are perhaps of greater importance than similar steps in the treatment of lesions elsewhere in the body. There

* Since the above notes were made two other patients with true tumor (glioma) have shown a positive Wassermann reaction.

has been a tendency to pay less attention to these steps in cranial surgery and to emphasize the treatment of the lesions themselves. Yet the control of hemorrhage from the scalp and bone, which, under increased intracranial pressure may be extraordinarily vascular, remains one of the most difficult features in cranial surgery. With its attendant shock, hemorrhage is one of the most potent factors in the high mortality generally attending cranial surgery and is responsible in the majority of cases for the adoption of a two-stage procedure. The element of time, so long as hemorrhage is satisfactorily controlled, is of little importance, and therefore in forming osteoplastic flaps, motor-driven have little advantage over hand-driven instruments, aside from lessening the manual labor involved. Nor are the difficulties in the approach to intracranial new growths confined to scalp and bone; for owing to increased intracranial pressure the dura may be under such tension, that the careless opening of this membrane results in the rapid herniation of the cortex through the defect and its rupture with all the attendant complications.

The problem of extirpating intracranial new growths is largely also a problem of the control of hemorrhage, but a problem different from that obtaining in the treatment of malignant tumors elsewhere; for, while in the latter we unhesitatingly occlude all large vessels supplying the lesion, in the former we must preserve vessels the occlusion of which might lead to extensive softening of the brain. Other important factors must be borne in mind. The removal of a tumor, simple in itself, owing to its proximity to or involvement of a vital center or structure, may lead to the death of the patient; or, because of its situation in the speech or motor centers, may leave the patient after its removal in a condition more deplorable than before.

One has merely to read statistical reports, and to recall some of the cases which come to the clinic secondhand, to realize that large, unsightly herniæ, often causing extensive paralyses and fungus cerebri, are too common, and aside from infection are largely the result of a too careless closure of the wound. In the prevention of these complications we believe the transplantation of fascia has been a great aid.

We are by no means satisfied that the control of hemorrhage from scalp, bone and cortex has been satisfactorily solved. Yet we have had, up to the present time, no deaths upon the operating table and no deaths from hemorrhage or shock. In 150 cranioplastic operations for brain tumor and epilepsy, a re-elevation of the bone flap has been necessary only once because of post-operative bleeding; and in the same number of cases a two-stage operation has been necessary but once because of hemorrhage. In 28 cases of partial or complete extirpation of the lesion the case mortality was 3 per cent. In this series there has been no post-operative pneumonia, a result due in large part, we think, to intratracheal anesthesia. We regret to say that in two cases superficial infections (stitch abscesses) occurred.

Types of Operation.—In the treatment of intracranial tumors only four types of operation need be considered; a decompressive craniectomy done for the relief of pressure

symptoms in cases of unlocalizable tumors; an osteoplastic resection for the exposure of cerebral tumors (often combined with a decompression); a cerebellar exploratory and decompressive craniectomy for tumors of the cerebellum and cerebellopontine angles; and the nasal or intracranial operation for the exposure of hypophyseal tumors. In the treatment of cerebral and cerebellar lesions we have followed the procedures as developed by Cushing, to whose writings reference may be made for details. (Keen's Surgery, etc.) The subtemporal method of decompression seems undoubtedly the operation of choice for the relief of pressure symptoms due to cerebral tumors; for, as its author has pointed out, the support and protection afforded by the temporal muscle and fascia limit the size of the hernial protrusion, and the operation, done over the relatively silent temporal lobe, avoids the paralyses attending defects made over the parietal and paracentral regions. Whether the subtemporal defect be made over the supposed side of the lesion or upon the opposite has, in our experience, made little difference so far as the relief of pressure symptoms is concerned; and it has been only in cases in which a left-sided exploratory craniotomy has failed to reveal a cortical lesion that a left subtemporal decompression has been done. In spite of great care in the formation of the defect, a temporary aphasia has followed a left subtemporal decompression in two instances.

In the treatment of hypophyseal lesions the nasal approach has been most strongly advocated and most frequently used. Cushing,* who has had the largest series of cases, in 124 operations upon 95 patients has used the nasal approach 111 times, the intracranial approach 13 times. Von Eiselsberg,* who perhaps has had the next largest series of cases, practically always employs the nasal approach. Frazier,† reporting the cases from the literature in 1913, found that 64 out of 74 cases had been operated upon by this method. Notwithstanding the overwhelming support in favor of this type of operation, the further development of hypophyseal surgery would appear dependent upon a satisfactory *intracranial* approach. The nasal operation, except in rare cases of hypophyseal cyst, is a purely palliative procedure; and, while comparatively simple, has the disadvantages of a septic approach, a very limited exposure of the region attacked, and a restricted field of usefulness. The intracranial operations thus far suggested (Krause,‡ Kiliani,§ Frazier,|| McArthur,¶ etc.) have been unsatisfactory, in that a more formidable procedure has resulted in but little greater exposure of the hypophyseal region than the nasal approach offers. We have employed now in six cases an intracranial operation which obviates many of the disadvantages of intracranial procedures thus far described, and has the advantage that it gives a wide exposure of the hypophyseal and chiasmal regions. This operation will be described in a subsequent communication.

One-Stage Versus Two-Stage Operations.—Whether an operation be conducted in one or two stages must be left to the individual preference of the surgeon; a preference dependent, in large part, upon the surgeon's mortality. Aside from the patient's aversion to a two-stage procedure, the dis-

advantage of operating in a non-virgin field, and the added dangers from a second anesthesia (pneumonia, etc.), from infection and its consequences (meningitis, fungus cerebri, etc.), and from other post-operative complications, would lead a surgeon to complete an operation at one sitting were his mortality low. Recent statistics indicate that, in spite of its disadvantages and added dangers, the two-stage operation is the operation of choice both in this country and abroad; and it is said by its adherents to be responsible for a lowered operative mortality. Very few statements are at hand to show the cause of operative deaths in brain-tumor cases; but that hemorrhage and shock, infections (meningitis), pneumonia, and respiratory paralysis (due to tumor pressure, sudden dislocations, cerebral edema, etc.) are the most common causes, is evident. Of these, hemorrhage with its attendant shock is the most important cause. Together with the occurrence of a tense dura, it is the troublesome factor in the approach to intracranial tumors and is responsible in most instances for two-stage operations. That it and the complications attending surgical operations in general enter largely into the mortality is indicated by the number of deaths following simply the approach to brain tumors, that is, the first stage. Krause,² reporting 154 cases of brain tumor operated upon within the 12 years preceding 1913, cites 21 cases operated upon *in one stage*, with a mortality of 65 per cent. Of the remaining 133 patients operated upon in two stages, 29 died at the end of the first stage (before the dura was opened), a mortality of 21.8 per cent. His average mortality in 104 cases of tumor extirpation, done in two stages, was 34 per cent; so that his greatest mortality occurred during the first stage. Von Eiselsberg,³ in the extirpation of 46 cerebral tumors, had nine deaths, six of which occurred after the first stage; and in 32 cases of cerebellar tumor, 17 deaths, nine of which occurred after the first stage.

It is not our purpose to urge the one-stage operation in preference to the two-stage procedure; but to indicate that the factors responsible for the adoption of the less satisfactory two-stage operation can be largely eliminated. Bleeding which resists all efforts for its control, a badly taken anesthetic, or an unusually tense dura, may determine one to abandon the operation for a second sitting. That this should be an exceptional occurrence rather than the rule has been demonstrated by Cushing; and our present series supports the view in favor of one-stage operations.* In 71 operations done upon 62 patients, a two-stage operation was necessary in but a single case, in which a mistaken X-ray diagnosis of osteoma of the skull led us to attempt to remove an area of extremely vascular hypertrophied bone before discovering the underlying tumor. None of the six deaths in this series could be ascribed to hemorrhage or shock; and in none of the patients that recovered was the condition such that a blood transfusion was deemed advisable. Possibly an unusually favorable series of cases has been responsible for the small number of two-stage operations; but

we believe that a careful control of hemorrhage during the approach and subsequently a careful closure of the wound have been the determining factors.

Anesthesia.—The occurrence of cardiovascular and respiratory disturbances of cerebral origin makes the administration of a satisfactory anesthesia more difficult in brain-tumor cases than in other groups of surgical cases. Labored respiration, cyanosis, coughing and straining increase greatly the difficulties of a cranial operation. Aside from its danger as a respiratory hindrance, cyanosis especially causes a great increase in the venous bleeding from the scalp and bone, an engorgement of the cortical vessels, and so great an increase in intracranial tension, that the opening of the dura becomes an exceedingly dangerous procedure. Especially, perhaps, in the cerebellar operations is cyanosis the matter of importance; for with tumors in the posterior fossa causing compression upon the medulla a little cyanosis may be sufficient to cause respiratory paralysis. So essential to the success of intracranial surgery is the administration of a smooth, even anesthesia, that the services of an expert have been considered necessary by surgeons interested in this field of surgery.

In the present series of cases ether alone has been used; and we have had an excellent opportunity of comparing either anesthesia administered by the usual drop method and by intratracheal insufflation. Watt's⁴ report includes this series of cases; and for details reference may be made to his paper. By the use of intratracheal insufflation, the difficulties attending anesthesia in brain-tumor cases have been very largely overcome; and in the last 35 cases in which this method alone has been used, a smooth, even anesthesia, without cyanosis, straining or coughing, has been the rule. Owing probably to the absence of cyanosis, hemorrhage has been distinctly less. The method allows the administration of a constant measured amount of ether, and therefore a constant depth of anesthesia. A striking evidence of this is the change we have noted in the character of our pulse charts. Even when the drop method is employed by an expert, the pulse chart is often represented by a rising and falling curve, due more often to varying depths of anesthesia than to operative manipulations. When the ether is given by the intratracheal method, the pulse chart is represented by a straight line, even in prolonged anesthetizations (three hours). Deviations from this straight line are of greater significance than changes occurring in the rising and falling chart of the drop ether method, and combined with blood-pressure observations they indicate more truly the effects of hemorrhage and operative manipulations. In addition to insuring a smooth anesthesia and to giving more certain information of the condition of the patient, the intratracheal method has other advantages. Among others, it relieves the anesthetist from the burden of holding the patient's jaw and other manipulations often necessary to insure easy respirations; so that he can devote himself more completely to observing the patient's condition. It removes him entirely from the operative field. It provides a satisfactory method of artificial respiration without change of apparatus, should

* It is possible that in the removal of cerebellopontine-angle tumors the two-stage operation may be preferable to the one-stage. Our experience with tumors in this region is not sufficient to warrant us in expressing an opinion.

respiratory paralysis occur. The services of an expert, while desirable, could, in the above series, but rarely be employed.

We have but a single observation upon the effects of multiple anesthetizations by this method. The one patient in whose case a multiple-stage operation was necessary was anesthetized three times at about 10-day intervals, with no untoward effects.

Local anesthesia (novocain, 1-400) has been used in only one case—a patient suffering from extensive pulmonary tuberculosis. The entire operation—an exploratory craniotomy for a subcortical cerebral lesion—was completed with surprisingly little pain. It is interesting to note that the only complaints of pain were made when, in reflecting the bone flap, the temporal muscle was pulled upon. The dura, supposed to be a sensitive structure, gave rise to no pain in this case when cut, tugged upon, or pinched. The cortex was entirely insensitive.

Control of Hemorrhage.—This most important factor has occupied very largely the attention of surgeons interested in intracranial surgery. Obviously, bleeding from such different structures requires a variety of means for its control, and often slower, more patient, and less certain methods than the clamp and ligature must be employed. It would serve little purpose to discuss the various means which have been described and used for the control of hemorrhage from scalp, bone, dura and cortex; for we have made use only of those which, although often inadequate, most nearly meet our needs. The subject is dealt with in the various text-books (von Bergman, Keen, etc.), and for many devices useful in controlling bleeding, especially from the dura and cortex, reference may be made to the paper of Cushing.¹⁵

The numerous forms of clamps, tourniquets, and sutures which have been described are an evidence that the control of bleeding from the scalp has not been satisfactorily solved. In a certain proportion of cases a well-fitting tourniquet is adequate and a perfectly dry approach possible. Very often, however, this is quite unsatisfactory, and bleeding occurs from arteries and veins presumably receiving blood from the skull. It ceases to be useful so soon as its pressure upon the skull at any point is released, a condition which often occurs when an exploratory craniotomy is converted into a decompression. In the closure of wounds it is a disadvantage. If it be loosened or removed before the closure is begun, hemorrhage from the wound margins is too severe; if retained until the closure is completed, we must depend upon the careful approximation of the wound margins to control hemorrhage—a not very safe procedure. Because of these disadvantages we have, in an increasing number of cases, discarded the tourniquet and resorted to the more tedious method of clamping each bleeding vessel, as the scalp incision, tourniqueted on its concave side by the hands of the assistant, is slowly made. The numerous clamps upon the concave side of the incision are well out of the operative field; those upon the flap side of the incision would be troublesome in subsequent manipulations. It is our custom, therefore, to elevate the temporal muscle from the base of the flap at the beginning of the operation, and place a temporary clamp resembling a stomach clamp across the scalp and muscle. This is made just tight enough to occlude the

vessels in the flap. The method is not ideal; but it assures a control of bleeding in the approach and, with the clamps upon the concave margin of the wound as a guide, enables us to place our sutures around the bleeding vessels during the closure. We have attempted in a number of instances to tie each bleeding point in the scalp incision; the procedure has prolonged the operation unduly, and has tended to invert the margins of the wound so as to make the subsequent closure more difficult.

In operations upon the cerebellum clamps alone meet the requirements; and literally hundreds must be used to satisfactorily control hemorrhage from the scalp and muscles in the vascular cases. Hemorrhage from the bone is best controlled with wax.

For active hemorrhage from the dura the encircling ligature or the placing of silver clips, as described by Cushing,¹⁶ suffices in the majority of cases. The middle meningeal, or its branches, are the vessels with which we have most often to deal, and usually these are readily controlled. Occasionally, when the upper margin of the bone flap approaches closely the median line, bleeding occurs between the dura and bone, presumably from the longitudinal sinus. Usually such bleeding may be controlled by a temporary pack of dry or moist cotton, or by a piece of muscle. In one case it was necessary to expose and suture the longitudinal sinus. The possibility of an abnormally placed sinus in the dura should be remembered. We have had a single experience—a wide venous lake in the dura over one cerebellar lobe which was so flattened by pressure as to be bloodless. Our usual opening in the dura was followed by an alarming hemorrhage, the source of which was at first not recognized and which was controlled with great difficulty.

Hemorrhage from the pial vessels, if slight, is most satisfactorily controlled either by pressure with cotton or with muscle; or with ligatures of fine silk or silver clips, if from vessels of considerable size. In the removal of a cortical lesion, the tumor is encircled by a double row of ligatures or clips, and the incision through the cortex carried between them; for the control of bleeding from subcortical structures, masses of cotton are temporarily used until the lesion is removed and the individual bleeding points are seen and stopped with ligatures or clips. It is remarkable how quickly the hemorrhage from the cavity left after removal of a lesion ceases when held in check for a few moments with dry cotton; a circumstance due more perhaps to the coagulating properties of the brain substance than to the cotton. In the removal of tumors from more or less inaccessible regions (*e. g.*, the cerebellopontine angle) we depend largely upon a temporary pack—an obviously unsatisfactory method. For securing deeply placed vessels of any considerable size, the silver clips have been most useful. In the intracranial approach to hypophyseal tumors the anterior cerebral artery has been torn twice; in both instances the resulting hemorrhage was successfully controlled with clips.

Treatment of Intracranial Tension.—Under conditions of increased intracranial tension, the opening of the dura becomes one of the most important steps in a cranial operation. If the dural tension is not relieved, the opening of the membrane may

result in rupture of the cortex with all its attendant difficulties and complications, or in the sudden dislocation of structures leading to respiratory paralysis. Relief of dural tension may be accomplished usually by one of four procedures having for their purpose the withdrawal of cerebrospinal fluid; ventricular puncture, lumbar puncture, tapping of the posterior median cisterna, and the gradual withdrawal of fluid between the meninges through a minute opening in the dura. Of these procedures ventricular puncture has perhaps the greatest field of usefulness, being applicable for the relief of dural tension in both cerebral and cerebellar explorations. For the relief of tension over either hemisphere the lateral ventricle is tapped with a blunt ventricular needle either through the operative field or through a separate opening in the skull. For the relief of tension over the cerebellum, the posterior cornu of either lateral ventricle is tapped through an opening in the skull a little above the transverse sinus and 1.5 cm. from the mid-line.

Lumbar puncture, as has been repeatedly pointed out, is a procedure attended by considerable risk to the patient; yet this risk must occasionally be taken in cases of "dry brain," in which no fluid can be milked out from between the meninges and in which ventricular puncture has failed. That it need only rarely be employed is indicated by the fact that only one patient in this series (suffering from a hypophyseal tumor) was subjected to a lumbar puncture during operation. The tapping of the posterior median cistern for the relief of tension over the cerebellum, and the withdrawal (milking out) of fluid from the intermeningeal space for relieving tension over the hemispheres, are done through a minute opening in the dura. In the former procedure the cerebrospinal fluid is discharged as soon as the wall of the cistern is opened; in the latter, it must be gradually expressed along some instrument, such as a grooved director, inserted underneath the dura.

Examination of the Exposed Skull, Dura and Cortex.—The superficial tumors, especially the dural endothelioma and osteosarcoma, may, as is well known, cause erosion and pressure atrophy of the overlying bone. It has been our experience to locate accurately subcortical tumors by the examination of the exposed bone; for they, in their early stages at least, exert their greatest pressure locally. So too, the appearance of the dura, its color, vascularity, opacity, or local thickening may indicate an underlying lesion. Careful examination of the cortex may be productive of a great deal of information. Encapsulated growths offer no difficulty in determining their limits; and usually the cortical infiltrating gliomata indicate their boundaries by color changes and differences in consistence on palpation. Yet in some cases the margins of these tumors are impossible to differentiate from the surrounding cortex. In the location of subcortical lesions palpation and aspiration are our most useful aids; occasionally the local flattening and widening of the convolutions over a growth give an indication of its presence. Palpation of the cortex is difficult and often misleading; in three cases, however, a subcortical tumor has definitely been palpated and subsequently removed. By the use of palpation and aspiration, nine subcortical cysts or cystic

gliomata have been discovered. In the discovery of subcortical cerebellar lesions, the comparative size of the two cerebellar lobes has been helpful.

Operability of Brain Tumors.—It should not be forgotten that, in speaking of the operability of brain tumors, we are dealing, for the most part, with malignant tumors; and that, because of anatomical and clinical difficulties, our chances of cure by surgical means are less than in malignant tumors elsewhere in the body. Yet if we except the metastatic tumors (carcinoma, sarcoma, etc.) and possibly the tuberculoma, the true cerebral tumors should, pathologically speaking, offer a better hope of cure; for, although prone to local recurrence, they do not tend to metastasize. The difficulty is that so many are subcortical and inaccessible; or they give so few definite symptoms that we are unable to make an early focal diagnosis. In the vast majority of cases the tumors exposed at the operating table are so large as to preclude the hope of successful extirpation.

The question of the operability of cerebral tumors has been approached from various points of view. Groups of statistics have been prepared showing the late results in cases of tumor extirpation (von Eiselsberg, Cushing, Sargeant and others); and it must be admitted that the results are still very unsatisfactory. Critical examination of patients dying as a result of operation or dying unoperated upon, with the idea of determining the chances of operative removal of the lesions, show a very small per cent of lesions favorable for surgical extirpation. Less enthusiastic observers have compared the survival period of cases untreated by surgery with cases subjected to operation, and find but little difference.

Although our chances of a cure by extirpation of the tumor are at present few, practically every operation may be converted into a palliative procedure; and in fully 50 per cent of all cases we may confidently expect an amelioration or total disappearance of pressure symptoms and a subsequent comfortable existence.

The indication for operation in practically all cases of brain tumor, and the favorable results of palliative operations in cases of unlocalizable tumors, are then quite clearly established. What attitude should be taken in the presence of a cortical or discovered subcortical growth, and how best it may be treated so as to prevent local recurrence, are questions not yet satisfactorily settled. Our comments indicate merely our present attitude and are open to the objection that they are based on our immediate rather than late results of surgical procedures.

Glioma.—This, the most common type of cerebral tumor, is least favorable for operative removal. Occasionally encapsulated, gliomata may be shelled out of their bed almost as satisfactorily as the endotheliomata. Others are comparatively hard tumors, and, although not encapsulated, have margins which can be more or less satisfactorily determined by palpation; they offer some hope of total extirpation, by the removal with them of as wide an area of normal cortex as possible. The cystic tumors, especially those with but a fragment of tumor in the cyst wall, also lend themselves to extirpation, the solid portion of the tumor being removed with the cyst wall. Least

favorable are the soft, sometimes gelatinous, infiltrating tumors, the margins of which cannot be differentiated from the surrounding cortex, and the ramifications of which cannot be followed in the subcortical structures.

With certain reservations, we have deliberately attempted the removal of gliomata whether cortical or subcortical; for we have wished to discover the possibilities in the removal of the different varieties of this tumor, and subsequently to determine the percentage of recurrences and the duration and degree of comfort of life after removal. The exceptions to this rule have depended more often upon the situation of the lesion than upon its character. We have thus far been unwilling to remove a large glioma from the speech area, if speech has in a measure been retained; and we are often doubtful whether or not to attempt the removal of a growth from the motor strip in the absence of paralysis; if the character of the growth leaves the possibility of its total removal in doubt. It is well known that intact nerve fibers may penetrate a tumor so that paralysis may be absent; but there seems little doubt that paralysis eventually occur. We have been impressed with the remarkably few cases in which, even with the removal of large tumors, paralysis have occurred. At the present writing we are unable to say from personal observation whether an incomplete extirpation of a growth is less satisfactory as regards comfort and prolongation of life than a simple palliative operation. The results of others would tend to support this view. Our immediate results have been satisfactory. The mortality in extirpations has been low, the post-operative paralysis insignificant, the relief from pressure symptoms prompt.

Since gliomata do not tend to metastasize (aside from the tumor infection of the meninges) our operative efforts need to be confined to the local condition. Since it is often so difficult to determine the margins of the growth, as wide an excision of the surrounding normal cortex should be attempted as is consistent with the least possible paralysis and the preservation of important cortical vessels. In closing the wound, the pial edges are sutured, if feasible.

Endotheliomata.—These are favorable, if not the most favorable, tumors for surgical removal. That the results have not been better has been due to the high operative mortality; for these growths are sometimes exceedingly vascular and their common occurrence in the cerebellopontine angle makes their approach difficult and the post-operative complications (respiratory paralysis) frequent. Although encapsulated tumors, they may be firmly attached by a pedunculated or sessile base to the meninges; and, unless the base or origin of the growth is removed, there remains the possibility of local recurrence. That this is of common occurrence is indicated by statistics. In addition to overcoming technical difficulties and avoiding post-operative complications, our efforts, then, should be directed to preventing local recurrence. In the case of tumors in the cerebellopontine angle this is very difficult, and often we must content ourselves with breaking off a tumor at its base, leaving some fragment behind. Over the cerebrum the problem is less difficult; and with the transplantation of fascia at our

command, we may and should remove with the tumor a wide area of attached dura.

Cysts.—These are, pathologically, perhaps not so favorable, but surgically (because attended by a much lower mortality) they are more favorable for treatment than the endotheliomata. They tend to refill after evacuation, and therefore simple withdrawal of the cyst contents should not be considered sufficient. Nevertheless, cases are known in which simple aspiration has resulted in a cure. It is usually possible to remove more or less completely the cyst wall, which appears as a soft, gelatinous structure easily separated from the surrounding brain. It is questionable whether iodine or other irritating substances should be used to provoke inflammation and subsequent adhesion of the opposing cyst walls. The procedure has its analogy in the treatment of cystic conditions elsewhere; but it would seem that the irritating effect of the substance would tend to a more rapid refilling of the cavity. We have had no experience with the treatment of parasitic cysts.

Our personal experience with other lesions has been too slight to warrant comment.

Transplantation of Fascia.—The transplantation of fascia lata has been a helpful procedure. Most ideally it has been used to cover large dural defects left after the removal of tumors that have arisen from or have been firmly attached to this membrane; or in cases in which both dura and bone flap have had to be removed. The area of dura which may be removed is almost unlimited; for from the lateral aspect of the thigh a piece of fascia lata as large in area as the ordinary bone flap may readily be obtained. In a recent case a piece of fascia was successfully transplanted into a dural defect 12 x 11 cm. in diameter.

The procedure has a further field of usefulness in cases in which subsequently to operative manipulations the dural flap cannot be satisfactorily closed over the protruding cortex. This is not of uncommon occurrence. The removal of a cortical or subcortical tumor is sometimes followed by a rapid edema causing the brain to herniate through the dural defect and making the closure of the dural flap impossible. The usual procedures under these circumstances have been a ventricular or a lumbar puncture, or to make a subtemporal defect in bone and dura and crowd the cortex through this defect as the margins of the dural flap are approximated. Whether or not a decompressive defect is deemed advisable, the transplantation of fascia in these cases would seem a better procedure and has been satisfactorily employed in a number of instances. Radiating incisions are made in the dural flap so as to produce a general protrusion of the cortex rather than a local protrusion, in danger of strangulation; after which the margins of the dural flap are approximated as far as possible without tension. Over the whole is transplanted a flap of fascia, the lower margin of which, in cases in which a subtemporal defect is deemed advisable, coincides with the upper margin of the bone defect.

In a single case in which a local collection of cerebrospinal fluid occurred over a subtemporal defect, necessitating frequent tapping (a condition simulating an arachnoidal cyst), the removal of the pseudomembrane and the transplantation of

fascia over the cortical protrusion promptly relieved the condition. It is possible that such a procedure might relieve a similar condition occasionally seen following cerebellar operations.

The transplantation of fascia has been very satisfactory in two cases in which a subtemporal decompression was inadequate for the relief of pressure symptoms, and in which the removal of the entire bone flap seemed advisable. A very large opening in the dura diminished the chances of strangulation of the cortex; and the transplantation of fascia over the dural defect gave, we believe, an added support to the scalp and perhaps helped to limit the size of the protrusion.

In the treatment of post-traumatic epilepsy with extensive adhesions between cortex and dura, we have in three cases excised the roughened dura and transplanted fascia into the dural defect.

In the present series we have transplanted fascia in nine cases. The fascial transplant has healed in perfectly in every instance. There has been no case of infection. In only one case have we had an opportunity of subsequently examining the transplant. In this case the old operative wound was reopened six months after the transplantation of fascia. The entire transplant was intact, vascular, and its structure, as indicated by the striations seen in the freshly exposed fascia lata, was preserved. The line along which it was united to the normal dura was almost imperceptible; but could be followed by the perfectly healed-in, black silk sutures. Most unfortunately, a fragment of the transplant removed for microscopic section was lost.

The technic, as we have used it, is simple. The transplant is merely spread over the defect and sutured to the dura with a series of interrupted fine, black silk stitches.

EXPERIMENTAL TUBERCULOUS MENINGITIS.

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Tuberculosis of the meninges in man is usually secondary to a tuberculous focus in some other part of the body. The prognosis in this condition is bad, the therapy futile.

Experimentally, to find an efficacious method of treating tuberculous meningitis requires as a prerequisite the production of a condition resembling that met with clinically. This is a difficult task, for, though in experiments on animal— a disseminated and miliary infection is readily brought about, lesions in the meninges fail to develop, perhaps as a result of the activity of the choroid plexus.

A survey of the literature reveals little, except that localized tuberculosis of the meninges has been produced by the direct introduction of tubercle bacilli into the nervous system, and that after the production of the local disease systemic invasion may occur.

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Manwaring¹ carried out experiments on dogs. He made a trephine opening in the skull, replaced the removed bone with a disc of paraffin and allowed the sutured wound to heal. At a subsequent time, an inoculation of bacilli was made by means of a long, blunt hypodermic needle passed through the coverings of the head, the paraffin disc and the frontal lobe of the brain, to the base of the skull. Tubercle bacilli of the human and of the bovine type, injected according to this technic, gave rise to the development of a tuberculous meningitis followed by paralysis and death. When, after the injection of the bacilli, suspensions of canine leucocytes were introduced into the subdural space, a delay in the development of the paralysis uniformly occurred, and the life of the animal was often prolonged. When the in-

¹ W. H. Manwaring: Jour. Exp. Med., 1912, XV, 1; 1913, XVII, 1.

fecting bacilli were of low virulence, the onset of the paralysis in the treated dogs was deferred for longer than seven months, whereas in the untreated control dogs paralysis developed within four weeks.

This paper records the results of a series of experiments made with the idea of attempting to find some measure of use in treating tuberculosis of the meninges. The observations were made on rabbits, inasmuch as monkeys and dogs were not available for the work. Healthy animals of approximately the same weight were chosen and all were kept under similar conditions.

There are certain disadvantages in the use of the rabbit. The spinal cord extends the length of the spinal canal, so that, when an injection into the spinal subdural space is attempted, it is difficult to avoid injuring the nervous tissue. Again, under normal conditions spinal fluid is present in so small amount that withdrawal of it by aspiration is not possible, and when the spinal canal is opened, not more than a drop or two is to be found. This paucity of fluid, noted even after inflammation of the meninges has developed, deprives us of the intravital means of estimating the progress of the infection and of determining the effect of treatment upon it.

In some of the experiments described, Manwaring's method of inoculation was used. With a small trephine a button of bone was removed from the skull of a rabbit. The opening thus made was sealed with paraffin, and, after closure of the wound with catgut sutures, healing was permitted to take place. After the lapse of from 5 to 12 days an injection of a suspension of tubercle bacilli was made through a long, slender needle that was passed through the skin, the subcutaneous tissues, the paraffin plug, and the brain, into the subdural space at the base of the frontal lobe.

This method, though readily carried out, is complicated and necessitates injury to the brain. Lumbar puncture was therefore attempted, and it was found surprisingly easy. The hair over the lumbo-sacral region was closely clipped, the skin then shaved and cleaned with tincture of iodine. The rabbit, after receiving a light ether narcosis, was placed on its abdomen and a small needle was passed between the spines of two lower lumbar vertebrae. Entrance into the spinal canal was recognized by a characteristic tactile sensation, and occasionally by a contraction of a hind leg or of the tail, if the spinal cord was touched.

The needle in proper position, a small Record syringe was affixed to it and the injection was made. A full-grown rabbit will readily tolerate the introduction of 2 cc. of fluid into the spinal canal, provided only slight pressure be used and the material be injected slowly. Generally, symptoms due to increased intracranial pressure developed during the procedure. The most constant of these were dyspnea, apnea sometimes lasting for 15 to 20 seconds, periodic respiration, retraction of the head and cervical rigidity of 20 to 30 seconds' duration, and generalized clonic spasms. In two instances, unilateral exophthalmos developed, to subside again within three minutes.

Spastic paralysis of one or both hind quarters was the only residual sign noted. It resulted from injury to the cord in nearly one-half of the animals in this series.

That material injected by lumbar puncture was distributed within the spinal canal was readily demonstrated. One and a half cubic centimeters of an aqueous solution of methylene blue, introduced under very little pressure through a needle inserted into the spinal canal in the lumbo-sacral region, spread within five minutes to the middle or upper thoracic region. The results of the experiments to be described show further that the inoculated material penetrates into the skull.

Thirty-five rabbits were utilized in making the following observations. Twenty received inoculations of the bovine type of tubercle bacilli, and 15 were injected with bacilli of the human type.

The strains used were:

(a) B1, a typical *Bacillus tuberculosis* of the bovine type, received from an outside source and of low virulence for rabbits.

(b) H39, a *Bacillus tuberculosis* of the human type, obtained through the courtesy of Dr. A. K. Krause, of Saranac Lake, and only moderately virulent for rabbits.

The bacilli were grown on the surface of glycerin agar and the suspensions for injection were prepared according to a constant technic. The growth of a culture two weeks old was suspended in 0.85% salt solution, thoroughly agitated with sterile glass beads in a mechanical shaker, and filtered through sterile cotton to remove coarse clumps. The resulting suspension was then diluted with salt solution to the approximate density of a 0.05% solution of lecithin in 0.85% salt solution.

From 1.0 to 1.5 cc. of such a suspension were slowly injected with very little pressure into the spinal canal, either through a needle inserted into the canal in the lower lumbar region, or into the cranial cavity according to the procedure of Manwaring already outlined.

The results of the inoculations are seen in the six protocols here given in detail. To avoid unnecessary repetition other experiments are not described.

PROTOCOLS.

Nov. 19, 1914. Rabbit 309. White female. Wt. 1800 gm. Lower back clipped, shaved and cleaned with tincture of iodine. Needle inserted into the spinal canal between the spines of the last two lumbar vertebrae. No fluid could be withdrawn by aspiration. Fifteen cc. of a suspension of B1, prepared as already described, were slowly injected while the animal was recovering from a light ether anaesthesia. There were no signs of injury to the spinal cord. For twenty minutes after the injection was completed, the rabbit remained dull and inert, lying on its abdomen with spread legs and making violent chewing movements.

Ten minutes later, except for the presence of a clonus in both hind quarters, the animal appeared normal and it continued so until six days later, when it seemed duller than usual.

Nov. 26, 1914. Marked emaciation. There was definite ataxia of the left hind leg.

Nov. 30, 1914. Animal weighed 1500 gm.

Dec. 3, 1914. There was no visible advance in the progress of the infection until this forenoon, when a striking change became manifest. The rabbit was prostrated, had a flaccid paralysis of the

fore legs and spasticity, but no paralysis of the hind legs. There were no other signs of meningeal irritation.

Dec. 4, 1914. The rabbit died after an attack of generalized clonic convulsions.

Autopsy.—Emaciated rabbit. Wt. 1400 gm. Examination of the abdominal and thoracic viscera and of the lymph glands showed no evidence of tuberculosis.

There was marked congestion of the meningeal vessels over the entire spinal cord, especially over the thoracic portion. The cerebral meninges likewise showed marked engorgement of the vessels, of maximal degree over the base of the brain and in the basal sulci. No tubercles were seen. There was a slight excess of opalescent fluid over the medulla and in the cerebellopontine angle. On section, no dilatation of the ventricles was found.

Smears from the meninges over the brain-stem and from the base of the brain showed many mononuclear cells, a few extracellular and two intracellular acid-fast bacilli.

Microscopic examination showed the presence of a meningeal (pial) exudate, rich in mononuclear cells and containing many polymorphonuclear leucocytes. The exudate extended into the substance of the cord along the intraspinal prolongations of the pia. There was also marked infiltration of the perivascular sheaths of the small arteries.

Nov. 20, 1914. Rabbit 310. Black and white male. Wt. 2160 gm. Lower back clipped, shaved and cleaned with tincture of iodine. The animal was etherized and a needle was inserted between the last two lumbar vertebrae into the spinal canal. No spinal fluid could be obtained by aspiration. One and a half cc. of the standard suspension of BI were slowly injected with little pressure into the subdural space. Immediately there developed coma, slowed and deepened respiration and a spastic paralysis of the left hind quarter. Recovery was complete within 35 minutes except for persistent paralysis of the left hind leg.

Nov. 23, 1914. The animal appeared normal except for the paralysis noted and for weakness of the right hind leg.

Nov. 27, 1914. In addition to the spastic paralysis there was loss of sphincter control and marked tactile hyperæsthesia. Emaciation marked; wt. 1700 gm.

Nov. 28, 1914. The symptoms had become much more severe in the previous twelve hours. There was extreme retraction of the head, cervical rigidity, intermittent generalized clonic contractions of the muscles and extreme hyperæsthesia of the skin.

Nov. 30, 1914. The foregoing symptoms persisted and the animal died on the eleventh day after inoculation.

Autopsy.—Emaciated rabbit in opisthotonic position. Wt. 1500 gm. Examination of the thoracic and abdominal viscera showed no evidence of a disseminated tuberculosis.

Examination of the central nervous system showed thickening and turbidity of the spinal meninges, especially over the thoracic portion of the cord, but no gross exudate. There was marked engorgement of the pial blood vessels over the spinal cord and the base of the brain, but no tubercles were seen.

Smears from the meningeal surfaces contained a few extracellular acid-fast bacilli, one bacillus in a large mononuclear cell and one in a small mononuclear cell.

On microscopic examination a meningeal exudate predominantly of mononuclear cells was found. There was marked infiltration of the perivascular tissue about the small arteries with small mononuclear cells, extension of the process along the prolongations of the pia into the cord, and a large fresh sub-pial tubercle over the dorsum of the lower thoracic cord. The structure of this tubercle was characteristic and showed beginning central necrosis. In the lumbar cord there was extensive involvement of the parenchyma. Over the pons there was an exudate similar to that found over the spinal cord.

Nov. 20, 1914. Rabbit 311. Black male. Wt. 2160 gm. The lower back was clipped, shaved and cleaned with tincture of

iodine. The rabbit was etherized, a needle was introduced into the spinal canal between the two lowest lumbar vertebrae and 1.5 cc. of the standard suspension of BI were slowly and gently injected. Coma promptly developed, with a short period of apnea, and there was transitory spasticity of the right hind leg. Within an hour recovery was complete, no evidences of injury to the spinal cord persisting.

Nov. 24, 1914. Yesterday slight ataxia of the hind legs developed and to-day they are somewhat spastic.

Nov. 30, 1914. The hind quarters have gradually become more paretic and now show almost complete spastic paralysis. The head is retracted and there is definite rigidity of the neck.

Dec. 1, 1914. The animal is dull and torpid; it lies on its abdomen and shows a spastic flexion paralysis of the hind quarters, loss of sphincter control, retraction of the head, generalized hypertonus of the muscles, hyperæsthesia of the skin and photophobia.

Dec. 3, 1914. The symptoms present 40 hours ago persist. In addition there are paralysis of all four extremities, opisthotonos and Cheyne-Stokes breathing.

Dec. 5, 1914. The animal was found dead in its cage.

Autopsy.—Emaciated rabbit. Wt. 1500 gm.

The general examination showed no evidence of tuberculosis except in the spleen, in which two pin-head yellow tubercles were seen.

When the vertebral column was opened the following changes were noted:

The blood vessels of the pia were engorged with blood throughout the length of the spinal cord. There was a slight excess of turbid spinal fluid present, but no gross tubercles were seen. Over the base of the brain, especially about the optic chiasm and the pons, the meninges had a gelatinous appearance.

Examination of stained smears made from the meningeal surfaces showed numerous large and small mononuclear cells and two intracellular acid-fast bacilli.

A study of microscopic sections showed an abundant meningeal exudate of mononuclear and polymorphonuclear cells, and perivascular infiltration with lymphocytes.

The inoculation into the peritoneal cavity of a guinea-pig of 3 cc. of the blood of this rabbit, aspirated from the heart 42 hours before its death, caused the development of typical tuberculosis.

Jan. 6, 1915. Rabbit 313. Gray male. Wt. 3215 gm. The lower back was clipped, shaved and cleaned with tincture of iodine. After the administration of a small amount of ether, a needle was passed between the two lowest lumbar vertebrae into the spinal canal and 1.0 cc. of a standard suspension of H39 was very slowly and gently injected. Signs of increased intracranial pressure promptly appeared—torpidity, deepening to coma, and slow periodic respiration. Recovery took place in 45 minutes, when it was noted that both hind quarters were paralyzed.

Jan. 22, 1915. The condition of the animal remains unchanged except for the emaciation which has been progressive. Wt. 2950 gm.

Jan. 29, 1915. During the past 24 hours loss of sphincter control, excitability and intermittent retraction of the head, have developed.

Feb. 1, 1915. Dull, difficult to rouse; respiration slow and deep. In addition to the signs already noted, there are persistent retractions of the neck, moderate generalized muscular hypertonicity and occasional clonic movements of the fore legs.

Feb. 3, 1915. Yesterday the animal lay in coma and this morning was found dead in its cage.

Autopsy.—Emaciated rabbit. Wt. 1750 gm.

There were no evidences of tuberculosis found in the general examination of the body.

The spinal meninges showed moderate engorgement of the vessels, but there was no excess of spinal fluid, and no tubercles were seen.

The pia over the convexity of the cerebrum showed marked overdistention of the vessels, and over the base there was definite "steaming" of the pia; but no gross exudate or tubercles were seen. Over the dorsal surface of the pons the pia was quite opaque.

Examination of stained smears, made from the meninges at the base of the brain, showed a few large mononuclear leucocytes and scattered acid-fast bacilli.

Microscopic examination showed the presence of a cellular exudate over the pia, and moderate perivascular infiltration with small mononuclear cells.

Feb. 13, 1915. Rabbit 329. Black male. Wt. 2400 gm. After routine preparation, and while the animal was slightly under ether, a needle was passed between two lumbar vertebrae into the spinal canal and 1.5 cc. of a standard suspension of H39 were slowly injected.

The only signs of pressure that developed were torpor, retraction of the head and dyspnea. These subsided after twenty minutes, and the animal seemed quite normal.

Feb. 23, 1915. No signs of infection appeared until this forenoon, since which time the hind legs have become spastic and paretic.

Feb. 24, 1915. There is now complete spastic paralysis of the hind quarters, and weakness of both sphincters. The rabbit is restless and rapidly emaciating.

Feb. 27, 1915. Four cc. of blood were aspirated from the heart for inoculation into a guinea-pig.

March 3, 1915. Very dull and inert most of the time, but at intervals there are periods of spontaneous restlessness, during which the animal emits loud cries and makes rapid convulsive movements of all four extremities and of the facial muscles.

March 4, 1915. The rabbit died in convulsions at 11 a. m.

Autopsy.—Emaciated rabbit. Wt. 1500 gm.

The general examination did not show any tubercles in the glands or viscera.

On opening the vertebral column an extensive extra-dural tuberculosis was seen extending along the bodies of the vertebrae of the upper sacral and lower lumbar regions. A thick firm caseating exudate lined the inside of the dorsal aspect of the spinal column, and on the ventral concavity of the vertebrae a hemorrhagic exudate, studded with tubercles, was present. This exudate was firmly adherent to the dura and pia over the spinal cord, both of which showed numerous milky grayish translucent tubercles. The vessels of the spinal and cerebral meninges were distended with blood. At the base of the brain there was a slight excess of turbid fluid and there were numerous translucent milky tubercles along the arteries.

Examination of stained smears made from the meninges showed numerous mononuclear cells, a few polymorphonuclear leucocytes and an occasional acid-fast bacillus.

Examination of microscopic sections showed typical lesions of tuberculosis—a meningeal exudate rich in mononuclear cells; perivascular infiltration with lymphocytes, a proliferative endarteritis, typical tubercles, and extension of the morbid process into the sulci.

The guinea-pig inoculated with the blood obtained from this rabbit five days before it died failed to develop tuberculosis.

Feb. 13, 1915. Rabbit 330. White male. Wt. 2250 gm. Lumbar puncture was made as in the experiments already described, and 1.5 cc. of a standard suspension of H39 were slowly and gently injected into the lumbar spinal canal. During the inoculation there were transitory jerking of the hind legs and tail, and apnea of ten seconds' duration. Within ten minutes the rabbit seemed quite normal and continued to appear so for ten days.

Feb. 24, 1915. During the last 20 hours a spastic flexion paralysis of both hind legs has slowly developed and there is hyperaesthesia to the touch.

Feb. 25, 1915. In addition to the signs already noted, there have developed emaciation, photophobia and anisocoria (the right pupil is definitely wider than the left).

Feb. 27, 1915. All of the symptoms have become more marked since yesterday. There is also retraction of the head, and whenever the animal is stimulated generalized clonic convulsions result.

Feb. 28, 1915. The rabbit was found dead in its cage.

Autopsy.—Emaciated rabbit. Wt. 1640 gm. Body in opisthotonic position. The right pupil was larger than the left. The general examination was negative.

The dura and pia over the entire spinal cord showed overdistention of the blood vessels, but there was no excess of spinal fluid. There were a few dewdrop tubercles scattered along the lining of the thoracic vertebrae. No evidence of injury to the spinal cord was found.

There were numerous punctate hemorrhages in the cerebral and spinal meninges and a few milky gray tubercles were scattered along the meningeal arteries of the cerebral convexity. At the base of the brain a striking picture of basilar meningitis was seen. From a point anterior to the optic chiasm and extending over the pons and medulla the meningeal vessels were engorged, the meninges thickened, and numerous gray and yellow tubercles were seen in clusters along the vessels. There was also a slight excess of opalescent fluid. The ventricles were not dilated.

Examination of stained smears of the free fluid showed fibrin, a few mononuclear cells and scattered acid-fast bacilli.

The microscopic sections showed essentially the same findings as those noted in the protocol of Rabbit 329.

The guinea-pig inoculated with 4 cc. of the blood of this rabbit did not develop tuberculosis.

These experiments demonstrate that the injection of tubercle bacilli into the spinal canal of rabbits caused the development of meningitis. The clinical syndrome produced was definite, and the symptoms were typically those of meningeal inflammation. The signs most constantly noted were dullness and coma, or restlessness, excitability and hyperaesthesia to touch and light, anisocoria, paralyses, muscular hypertonicity, even opisthotonos.

The symptom-complex differed in animals that were given the same dose of bacilli, but it varied more constantly in direct proportion to the number and virulence of the infecting organisms.

The incubation period of the disease due to the bovine type of bacillus varied from 8 to 15 days; the latent period following infection with the human type was from 7 to 20 days.

The onset of symptoms was sudden, following a period of progressive emaciation. The duration of the disease due to the bovine type of bacillus varied from 9 to 14 days, as contrasted with a duration of 16 to 28 days of the infection due to the human type bacillus. In both types of infection the result was fatal.

After infection of the meninges with either variety of the organism, a generalized tuberculosis may develop. In a series of 12 experiments with bacilli of the bovine type, a general infection developed twice, and in a similar series with the human type it occurred once. These results confirm Manwaring's experience.

Worthy of note were the frequent occurrence of a basilar meningitis and the distribution of tubercles along the blood vessels. By what mechanism or along what route the bacilli reached the meninges of the base of the brain is a matter of speculation, for the injection of stains into the spinal canal showed that under the experimental conditions the material introduced was not mechanically made to enter the cranial cavity.

A possible explanation is that the bacilli caused a direct infection of the lymph spaces of the meninges and were disseminated along the cerebrospinal lymph vessels. On the other hand, the development of tubercles along the blood vessels and the production of endarteritis indicate a hematogenous spread of the organisms.

After it had been found that tuberculous meningitis could be produced in rabbits, and after the incubation period, the symptoms, course and outcome of the disease had been established, an attempt was made to modify the course and prognosis of the infection by treatment.

(a) The intraspinal injection of "albumose-free tuberculin."

During the latent period of meningeal tuberculous infection, from 1.0 to 20.0 mg. of albumose-free tuberculin were injected into the spinal canal at intervals of 2, 3 or 7 days.

In none of the six animals treated were any beneficial results noted. In fact, the reverse seemed true. The symptoms seemed to be aggravated and the infection was more rapidly fatal. At autopsy, too, a greater degree of meningeal congestion and more numerous meningeal petechiæ were found than in the untreated control animals.

(b) The intraspinal injection of "tuberculinized" serum.

The procedure of Swift and Ellis of injecting salvarsanized serum into the subdural space in the treatment of syphilis of the nervous system has given such promising results that a similar procedure was tested upon rabbits suffering from meningeal tuberculosis.

One and a half cubic centimeters of undiluted albumose-free tuberculin were injected into the ear-vein of a normal rabbit, and from 45 to 60 minutes later 5 cc. of blood were aspirated from the heart. The blood was allowed to coagulate, and after three hours the serum was removed by centrifugalization. Six rabbits, which had received an intra-meningeal injection of tubercle bacilli 20 hours before, were each given an intraspinal injection of 1.0 to 2.0 cc. of this serum. The treatment was repeated at intervals of 24 and 48 hours.

The results of this procedure were completely negative. The onset of the symptoms was not delayed, nor was the lethal outcome deferred or prevented.

(c) The intraspinal injection of the serum of tuberculous rabbits.

The auto-serum of rabbits suffering from tuberculous meningitis, and the serum of rabbits suffering from generalized tuberculosis, when injected into the spinal canal had no beneficial influence on the course of meningeal tuberculosis.

(d) The intraspinal injection of leucocytes from rabbits.

Fresh leucocytes of the rabbit were obtained and prepared according to the technic described by Opie.²

One-half cubic centimeter of turpentine was injected into the pleural cavity of a normal rabbit and a similar injection was made three days later. On the fourth day the exudate was removed by aspiration and discarded. The newly formed leucocytic effusion was then withdrawn into an equal volume of 1.5% solution of sodium citrate. It was then filtered through sterile gauze, centrifugalized, washed twice with 0.85% salt solution; and a 50% suspension of the washed cells in salt solution was prepared. The suspension consisted of polymorphonuclear and mononuclear cells with a variable number of red corpuscles. Before injection the sterility of the suspension was determined by culture.

From 1.0 to 1.5 cc. of such a suspension were injected into the spinal canal of rabbits that had been given an intraspinal injection of tubercle bacilli from 24 to 72 hours before.

One of the six animals so treated did not develop symptoms of meningitis until seven days later than the control animal, and lived for 40 days. The other five rabbits showed no benefit as a result of the treatment, and all showed essentially the same pathological findings as did the controls.

SUMMARY.

1. The introduction of tubercle bacilli into the spinal canal of rabbits leads to the development of meningitis.

2. Tuberculous meningitis in rabbits presents a fairly typical clinical picture and leads to a fatal issue.

3. The lethal outcome of the disease in rabbits was not prevented by the intraspinal injection of the albumose-free tuberculin, tuberculinized serum, the serum of tuberculous rabbits or a suspension of rabbit's leucocytes.

The ready production of meningitis in rabbits by the intraspinal injection of infectious material suggests the use of such a method to identify the nature of a meningeal infection in man. It would be a simple procedure to introduce into the spinal canal of a rabbit 1.0 to 2.0 cc. of the spinal fluid of a patient thought to have tuberculous meningitis, and in a few days examination of the rabbit's meninges might give evidence of the tuberculous nature of the patient's disease.

² E. Opie: *Jour. Exp. Med.*, 1908, X, 419.

JOHNS HOPKINS HOSPITAL BULLETIN.

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A TREATMENT FOR PRURITUS ANI.

By HARVEY B. STONE, M. D.

As is of course well recognized, pruritus ani is merely a symptom and not a disease. Without discussing exhaustively its etiology or pathology, it may be said that the cause of the distressing itching is often found associated with one or other of several varieties of local lesion—such as hemorrhoids, pinworms, eczema—or in some constitutional disturbance of which diabetes may be mentioned as an example. Obviously, where the cause is known, the principles of treatment will be determined by the particular nature of this cause, and it is not the purpose of this paper to discuss such cases. There remain, however, the numerous and most difficult cases in which no causative factor can be definitely discovered and which are grouped under the term “idiopathic pruritus.”

Various theories—acid secretions, latent infection with special types of organisms, central and peripheral nerve disturbances—have been advanced to account for the condition. No less various treatments have been employed for its alleviation. The whole gamut of ointments, powders, lotions and irrigations have been employed with varying, but never general success. Cauterization, X-ray exposures, and vaccines have furnished more recent attempts to solve the problem. Operative measures, such as the Ball and Lynch procedures for division of the peripheral cutaneous nerves, have been employed. The fact that the latter have a certain field of usefulness and popularity is in itself evidence of the extent to which the patient is willing to go in seeking relief. One who has listened to the histories of such cases, with long months and years of intolerable annoyance and distress, broken rest, lost sleep, and impaired health, will feel that the attempt to improve our methods of attack upon this condition is not an unworthy field of endeavor. It is the purpose of this paper to make a preliminary report of such an attempt.

The success of alcohol injections for producing localized lasting anæsthesia, in facial and other forms of neuralgia, suggested the application of the same principle to the abolition of unpleasant sensations from the anal and perianal regions. The alcohol, of course, produces its effect by destruction of the nerve fibers with which it comes in contact. Hence, in essential principle, such a treatment is quite analogous to the Ball and Lynch operations referred to above, in which the cutaneous nerves are destroyed by direct mechanical division, instead of by chemical attack. The alcohol method presents certain definite advantages that will be referred to later; there are certain possible disadvantages, also, that will be considered at once. Since there is no selective action of alcohol, by which motor nerves are spared, and only sensory ones are injured, one might expect a loss of sphincter control, if the injection were allowed to come in close contact with the motor branches to the muscles. Moreover, an injection of a substance causing tissue destruction, if too superficially placed, might be expected to cause a slough and resultant ulceration.

In order to test these possibilities by actual experiments, alcohol injections were made into the anal region in dogs, the depth of the introduction being varied. Without detailing the protocols of experiments, the following facts were clearly proved. Alcohol injections will produce complete local anæsthesia. If introduced deeply enough to come in contact with the motor nerves, sphincter paralysis and resultant incontinence are produced. If introduced quite superficially—that is, within the skin itself—superficial sloughs are caused. It is quite possible, however, and not very difficult, to produce anæsthesia without sphincter paralysis or skin ulceration; this effect is brought about by introducing the needle entirely through the skin, but injecting the alcohol immediately under the skin and never more deeply.

The method has been tried by Dr. Arthur Hebb and myself in the dispensary of The Johns Hopkins Hospital and in our private practice on 17 cases so far, during a period covering less than two years. The facts observed are as follows. With the technique employed there is not much pain associated with the injection. There is some soreness during the first 24 hours, after which the only subjective sensation remarked is numbness. The itching is immediately abolished and the area injected is largely or completely anæsthetic. No case so far has shown the slightest evidence of disturbance in the action of the sphincter. There were several cases in which small superficial sloughs resulted, but these all healed promptly and without difficulty. They were due to faulty technique in placing the alcohol too superficially, a fault due to the careful avoidance of too deep an injection and to the fact that the folded, irregular surface of the skin about the anus renders it much more difficult to keep the injections at a uniform depth than would be the case were the surface level. How long the freedom from itching will last is not known. One patient has returned for a second injection, eight months after the first, for a recurrence of itching. All of the patients seemed much gratified with the results obtained, so far as we were able to follow them. An interesting change is to be noted in the physical appearance of the skin after a patient has received this treatment. The skin in typical cases of severe pruritus is thrown into thickened folds and ridges; it looks oedematous and grayish-white, with red scratch-marks and superficial fissures radiating from the anus, and feels stiff and indurated. A few days after an alcohol injection the folds become less pronounced and rugged; the color becomes more that of normal “flesh-color” and the scratch marks disappear. In short, there is a return to the normal appearance of the skin in this region.

The technique of injection is quite simple. The area in which the itching is complained of is carefully noted from the patient's description, and indeed is usually well marked out by the characteristic features just described. Under general or local anæsthesia, the injection is then made so that this whole

area is anæsthetized. In nearly all the cases here reported, a local anæsthetic, usually novocain (1 per cent) or quinine and urea hydrochloride (1 per cent), has been employed. This form of anæsthesia has proven quite satisfactory. The syringe is filled with alcohol (95 per cent) and the usual fine hypodermic needle used for the injection. The needle is carried entirely through the skin vertically and then is inclined sharply to the side so that it lies nearly parallel to the skin surface. When the needle is properly inserted in the subcutaneous fat, it can be moved fairly freely from side to side under the skin and can be felt moving with the finger placed over it. If this freedom of movement is lacking, the needle is probably engaged in the corium, and if injections are thus made, sloughs may be expected to result. With the needle properly placed the whole area involved is injected, enough alcohol being used to underlay the area thoroughly. The injection may be carried up to the

margin of the anus, but we have never injected the anal canal itself, nor have we so far had reason to believe that this would have improved the results. Of course, before any injection is made, the skin is cleaned up as for any other operative procedure.

This method accomplishes practically the same thing as the operative treatment for pruritus, and is indicated in those cases of great intensity in which the usual measures have failed. It has certain distinct advantages over the operative procedures. It is safer—there is no undermined skin with impaired circulation, with a potential dead space under it, in an area impossible to keep clean. It is quicker. It entails no dressings, stitches, or other post-operative annoyance to physician or patient, and no hospital expense. It is quite as likely to be enduringly satisfactory, and presents no greater possibilities of trouble.

A REVIEW OF THE LIFE AND WORK OF JONATHAN LETTERMAN, M. D.¹

By JOSEPH T. SMITH, M. D.

I esteem it a privilege, and it certainly is a pleasure, to be permitted to present to this club a brief review of the life and work of my uncle, Jonathan Letterman.

It seems especially fitting, in view of the war now waging, that we should have our attention directed to one who was able to accomplish so much in mitigating the horrors of war and whose methods are used to-day by the struggling nations of Europe.

Surgeon Clements, who was intimately associated with him as assistant medical director, says in his "Memoir of Jonathan Letterman, M. D." (p. 1): "It is the purpose of this memoir to perpetuate the name and to honor the memory of an officer, who effected an organization of the medical department of an army in the field, that not only contributed in a large degree to the discipline and efficiency of the foremost army of the Republic, but also robbed war of its horrors; who left behind him for the use of those to come the record of the means by which these noble ends may be again achieved; and who in rendering this great service to his country added a brilliant page to the record of the humane character of his profession."

Jonathan Letterman was born in Canonsburg, Pennsylvania, a small town near Pittsburgh, December 11, 1824.

His father, Jonathan Letterman, was an excellent physician and skilful surgeon. I remember hearing his mother, who was for many years an inmate of our house, tell of the sensation produced when her husband ligated an artery of the neck.

His mother was a daughter of Craig Ritchie, of Canonsburg, a man of character and influence; she was very fond of telling us of how, on more than one occasion, she saw her father walk-

ing with General Washington on the bank of Chartiers' Creek, a small stream near the town, discussing the financial condition of the young nation.

Dr. Letterman was well educated; a private tutor was provided for him until he was able to enter Jefferson College, Canonsburg, at that time one of the foremost in the country, which he did in 1842 and from which he graduated in 1845.

His medical education was obtained at the Jefferson College in Philadelphia and he received his degree there in 1849. In June of that year he passed the examination of the Army Medical Board and was appointed assistant surgeon.

He was ordered to Florida where he served in the campaigns against the Seminoles. While there he collected and preserved many specimens of the snakes, lizards, etc., in which the country abounded. This collection he sent to my father's house, together with beautiful articles of bead-work made by the Indians, all of which were a great delight to me.

In March, 1853, he was sent to Fort Ripley, Minn., and May, 1854, found him with the troops on their march from Fort Leavenworth, Kan., to New Mexico.

He was in service at Fort Defiance among the Navajos. I recall the curios he sent to our house, blankets and bead-work of the tribe.

He was engaged with Col. Loring in his expedition against the Apaches.

In 1859 he was on duty at Fort Monroe, Va., and the next year, 1860, he was ordered to California and was with Major Carleton in his expedition against the Utes.

In November, 1861, he came to New York with the California troops and went on duty with the army of the Potomac.

In May, 1862, he was appointed medical director of the department of West Virginia and in July was promoted to the rank of surgeon.

¹ Read before The Johns Hopkins Hospital Historical Club, January 10, 1916.

These 13 years' experiences were destined to be of great service to him in the trying months about to follow. The time, during most of those years, was spent at frontier posts and in campaigns against the Seminoles, Navajos, Apaches and Utes; many hardships had thus to be endured and resourcefulness was developed.

"In obedience to orders from the War Department," he reported on the first day of July, 1862, to Major-General McClellan at Haxhall's Landing for duty as medical director of the army of the Potomac and assumed his work on July 4.

Surgeon-General Hammond in making the appointment wrote to him (Clements, p. 3): "In making this assignment I have been governed by the best interests of the service. Your energy, determination, and faithful discharge of duty, in all the different situations in which you have been placed during your service of 13 years, determined me to place you in the most arduous, responsible and trying position you have yet occupied." He closes: "And, now, trusting to your possession of those qualities without which I should never have assigned you to the duty, I commit to you the health, the comfort and the lives of thousands of our fellow soldiers who are fighting for the maintenance of their liberties."

That Dr. Letterman took this letter to heart and did possess the qualities necessary to accomplish the task it will now be our purpose to show.

Upon taking charge, the new director found the supplies almost exhausted; but few hospital tents were available, the ambulances were in a bad condition, the number of medical officers was too small for the service and it was not possible to obtain reports of the sick and wounded. The troops had been through the most trying experiences. Scurvy prevailed, a disease greatly dreaded because it so undermined the strength and depressed the spirits of the troops, thus reducing the efficiency of the soldiers. Owing to the conscientious and skilful labors of the medical director and his assistants, the conditions just noted were so far improved as to give time in which to consider the whole subject of the care of the sick and wounded; and Dr. Letterman at once addressed himself to the task.

The most urgent claim upon his attention was the care of the wounded. He says (Recollections, p. 22): "The subject of the ambulances became, after the health of the troops, a matter of importance. No system had anywhere been devised for their management. They were under the control both of medical officers and quartermasters, and, as a natural consequence, little care was exercised by either." Under his "order" issued August 2, 1862, the ambulances were taken from the immediate control of medical officers, so as not to interfere with their duties as surgeons, and placed under the care of special officers, but under such medical supervision as to make them efficient and available. Time will not permit of a further description of the plan; the "order" embraced 16 sections and was so carefully prepared as to all the details that but little modification was required when it was made "An Act of Congress" in 1864. That we may fully

appreciate what the "order" and its accomplishment meant, let me quote from Lequeuse, who in 1861 wrote (Clements, p. 5): "The removal of the wounded from the battlefield and their transportation to the hospitals is the most defective part of the medical service. Even now, after the great wars of the end of the last century and the beginning of the present . . . this important service (in the French Army) is delegated to no particular person . . . when the wounded fall in the ranks, there are none . . . to carry them off except their own comrades." And the French Army at that time was the model army of the world.

The second of the great changes he brought about was in the method of supplying the army with medicines, dressings and medical material. Dr. Clements says (p. 9): "He (Dr. Letterman) reduced by careful selection the amounts of medicines and materials to be carried, lessened the number of wagons required to transport them to nearly one-half . . . and gave simplicity, compactness and efficiency to the whole service of supply." Dr. Letterman says in his book (Recollections, p. 51): "Hitherto medical supplies for three months had been furnished, directly to regiments, and no wagons allowed expressly for their transportation . . . not infrequently all the supplies of a regiment were thrown away by commanding officers, almost in sight of the enemy, that the wagons might be used for other purposes. The details of the new arrangement were published in a circular dated October 4, 1862, and no material change in its requirements was ever found necessary, the completeness of the plan having been at once demonstrated" (Clements, p. 9).

The third change inaugurated was a system of field hospitals, in the form of an "order" issued October 30, 1862, and it, like the others, was so complete in all its details that but few changes were required when it was put to a practical test. These hospitals were to care for the sick and wounded on or near the field of battle. None such, so far as is known, existed at that time in our armies. Their design was to relieve the immediate dangers of the wounded and in the case of those slightly disabled to put them speedily into a condition to return to the firing line.

An ambulance system, a supply system and a field hospital system were thus inaugurated: these three systems were but parts of a whole, designed to work together, so that out of their combined actions a complete scheme for the care of the sick and wounded might result.

He not only devised the means, but labored unremittingly to make them effective. That he was careful and painstaking is shown not only by the results obtained, but by the fact that so few changes were found necessary in their practical application.

In addition to working out the above problems Dr. Letterman gave close personal attention to the health of the troops, in combating scurvy, in looking after the sanitary conditions and healthful location and arrangements of the camps. He writes (Recollections, p. 46): "I established shortly after this battle (Antietam) two large camp hospitals. . . . These were the first of the kind attempted in this country. . . . For

the results of that battle gave additional evidence of the absolute necessity of a full and constantly renewed supply of fresh air to a wounded man." He experienced much difficulty in overcoming the prejudices against open camp treatment.

The lack of reports of the number and condition of the sick and wounded gave him great concern. He issued special blank forms for making such reports and in the "order" requiring them he says (Recollections, p. 115): "The knowledge which the officers of this department have had and may yet have opportunities of gathering, is of such a character and of such an extent as will, when made known, go far toward filling the hiatus which exists in our branch of the science in which we are now engaged—military surgery; and it is hoped that they will not permit these opportunities . . . to pass without availing themselves of the advantages which they afford." He gave specific directions for the collection and preservation of specimens of gun-shot wounds for the Army Medical Museum.

He made an effort to have established in Washington a hospital for venereal diseases.

He labored with an intelligent endeavor to better the condition of the army; he had the men critically examined, if they complained of being sick; those with slight ailments were quickly cured and sent to their work, while those malingering were detected and held for duty; in this way the efficiency of the army was still further increased.

To protect the ambulances from being invaded by those who had no right in or about them, he established a system of passes.

He examined the requisitions, both medical and surgical, in order "to reduce the waste which took place when a three months' supply was issued to regiments, to have a small quantity given them at one time, and to have it replenished without difficulty." (Recollections, p. 51.) Upon one occasion he purchased a large amount of jellies, fruits and poultry for the use of the sick, thus carrying out his letter of instructions, to provide for the comfort of the troops.

It must be remembered that all these manifold changes, and more could be noted, were brought about while the army was engaged in warfare and that most actively.

As a result of his labors and those of his assistants, the army which in July, 1862, had a sick roll of (estimated) 20 per cent, had this reduced in the early part of 1864 to about 3 per cent. (Recollections, p. 183.)

It is not necessary to take up your time with an account of the care and management of the sick and wounded in the present war. The instructive and interesting letters, reports and correspondences from the front in the British Medical and other journals are more or less familiar, but one or two quotations from Dr. Letterman's "orders" might not be out of place as showing how closely his plans are followed; in fact they are almost the same, except in the more rapid removal of the wounded in automobiles and their better care in the well-equipped trains. In the 4th section relating to ambulances we read (Recollections, p. 25): "He will institute a drill in his corps, instructing his men in the most easy and expeditious method of putting men in and taking them out of the ambulances, taking men from the ground and placing them on

stretchers." In his "order" relating to field hospitals he says (Recollections, p. 58): "Previous to an engagement there will be established in each corps an hospital surgeon for each division. He will detail another assistant surgeon whose duty it shall be to keep a complete record of every case . . . the seat and character of the injury, the treatment, the operation, if any be performed, and the result, which will be transmitted to the medical director."

In October, 1863, he married Miss Mary Lee, of Virginia, a lady he met for the first time, when, tired and hungry from the battlefield of Antietam, he and some of his staff dined at her house, she waiting on the table. On the occasion of their marriage, the medical officers of the army of the Potomac presented him with a handsome service of silver.

In December, 1863, he requested that he be relieved from duty and wrote (Recollections, p. 184), "It is evident no military movements can be made by either army. . . . The medical department has been fully organized in all its branches. . . ." A memorial was presented to the Committee on Military Affairs of the United States Senate by the principal medical officers of the army urging "that he be honored with the rank and rewarded with the emoluments granted to the heads of other staff departments."

Upon retiring from the army of the Potomac, he was assigned to duty as inspector of hospitals in the department of the Susquehanna; here he remained until December, 1864.

Mr. Thomas A. Scott, the well-known president of the Pennsylvania Railroad, made him a very flattering offer to take the superintendency of a commercial company in southern California. His friends urged him to remain in the army, but he decided to resign. He left the army December 22, 1864, and entered the service of the company, but, as it failed to fulfil the hopes of its friends, he left it and took up his residence in San Francisco.

In 1866 he wrote a book, the title of which explains its purpose, "Medical Recollections of the Army of the Potomac."

He was elected coroner of San Francisco in 1867 and re-elected for a second term.

On December 4, 1871, he retired to private life. A chronic intestinal trouble from which he had long suffered combined with the shock occasioned by the death of his wife, November 1, 1867, so undermined his health that he was not able to withstand an illness in 1872 and he died March 15 of that year, being a few months over 47 years of age. He was buried in San Francisco by the side of his wife; a few years ago his elder daughter had the bodies removed to the National Cemetery at Arlington, so that he now rests from his labors in a grave which overlooks the Potomac, whose army he loved and served so well.

His simplicity, his modesty, his direct speaking and frank manner, his kindheartedness and consideration for others, combined with an unselfish nature and generosity in according praise when merited, made him hosts of devoted friends, and it was doubtless the possession of such qualities that enabled him to carry to a successful issue his plans for the good of the army in the field. Dr. Clements says that Dr. Letterman's

admiration of his corps of surgeons was great, and his confidence in them unbounded and "he omitted no opportunity to recognize and commend them."

That he had the good of the army at heart is shown by the following quotation from his "orders" (Recollections, p. 13): "Sleep during the day will not compensate for the loss of it at night, and I suggest . . . that the men be allowed to sleep until sunrise and that they have their breakfast as soon as they rise."

In one of his "reports" he says (Recollections, p. 98): ". . . the duties of medical officers are not confined to prescribing drugs, but it is also their duty, and one of the highest importance, to preserve the health of those who are well. . . . The prevention of disease is the highest object of medical science," and again (Recollections, p. 122): "A corps of medical officers was not established solely for the purpose of attending the wounded and sick . . . but the labors of medical officers cover a more extensive field. The leading idea, which should be constantly kept in view, is to strengthen the hands of the commanding general by keeping his army in the most vigorous health, thus rendering it in the highest degree efficient for enduring fatigue and privation, and for fighting." "I had," he says, "a twofold object in perfecting the physical condition of the troops. First, that the commanding general should have an army upon whose health he could rely. Second, that those who might be wounded should be in a condition to bear the shock and the operation, the suppuration, and the confinement, with every prospect of recovery." These quotations will, I think, suffice to show the underlying principles which guided him.

Last month in this room before the Medical Society, Dr. Richard P. Strong, of Boston, gave a very instructive and interesting account of his efforts in overcoming the typhus epidemic in Serbia in 1915. These two Americans, Drs. Letterman and Strong, the former in devising plans for the care of the sick and wounded, and the latter in teaching us how speedily to stamp out typhus fever, have rendered inestimable benefits to suffering humanity and to warring peoples.

Two surgeons, whose names are familiar to all in this audience, ought to be mentioned and some of their experiences noted before we close, as they give an insight into the conditions under which Dr. Letterman labored, and incidentally of his association with them. Dr. W. W. Keen in his "Addresses" (p. 421) says: ". . . During the entire engagement (first battle of Bull Run) I never received a single order from either . . . medical inspector, the surgeon of my regiment or anyone else. . . . My experience in this battle is a good illustration of the utter disorganization or rather want of organization of our entire army at the beginning of the war. . . . Not long after taking charge (of Eckington Hospital) on Saturday afternoon, about 4 o'clock, I received an order to report at the office of Dr. Letterman. . . . I had so little experience in army orders that I almost trembled at the formal and peremptory character of the order." He says, again, (p. 430): "What we did not have in those days was almost more noticeable than what we did have. . . . There were no

hæmostatic forceps. . . . We had no hypodermic syringes. . . . We had no aspirators. . . . We had no clinical thermometers." Dr. Garrison in his "Life of John S. Billings" cites the following passage (p. 20): "I (Dr. Billings) began service and had three things with me that none of the other surgeons had. A set of clinical thermometers like those Dr. Keen talked about, a straight one and one with a curve; a hypodermic syringe and a Symes staff. . . . The hypodermic syringe was in constant requisition. The clinical thermometer was troublesome and was not used very much. . . . One day in the spring of 1862 I was in the hospital office, when two men walked in, one a large man with an air of importance, the other a small man who had said very little. . . . I then learned that my callers were Dr. Hammond, surgeon-general, and Dr. Letterman, medical director of the army of the Potomac." "On March 31, 1863, Dr. Billings reported for duty to Surgeon Jonathan Letterman . . . who had achieved a brilliant reputation by his effective work in the reorganization of the medical department of that army. . . ." (Garrison, p. 30).

Within a quarter of a mile of San Francisco Bay . . . located so as to receive the sea breezes through the Golden Gate, there stands a government hospital in which no department of the healing art fails to contribute its quota towards making the institution a veritable "general hospital." The buildings are modelled on the Paris Lariboisière, those for the sick being one story and arranged on the pavilion plan for 40 patients each, five surgical and four medical wards with a well-equipped operating room in a separate building. The hospital has the full modern equipment of laboratories, kitchens, baths, special detention and hydrotherapeutic wards. The hospital is an independent military station . . . its laboratory is extensive and well equipped, and makes the bacteriological and chemical examinations for the military service of the entire Pacific Coast. Captain Weed has sent me a very interesting account of the hospital and he closes by writing: ". . . By a general order of the War Department dated November 13, 1911, the hospital is hereafter to be designated the Letterman General Hospital in honor of the late Major Jonathan Letterman, surgeon, United States Army, who effected the organization of the medical department of the army of the Potomac during the Civil War.

The Letterman General Hospital is a fitting memorial to an officer who gave the best years and service of his life to caring for the sick and wounded, and nothing would rejoice him more than to have his name linked with such an institution.

DISCUSSION.

DR. H. M. HURD: We are under great obligations for this paper, and especially for those pleasant touches which brought Dr. Keen and Dr. Billings into contact with Dr. Letterman. I hope that everyone here who has not already done so will read the charming biography of Dr. Billings by Dr. Garrison. He was a young surgeon who happened to pass an unusually good examination before the Army Medical Board, which fact, if I remember correctly, was what attracted the attention of Dr. Letterman and induced the latter to visit the hospital of which Dr. Billings happened to be in charge on the Virginia side of the Potomac. He arrived unannounced in company with Surgeon-General Hammond, and it

finally appeared that he wished to see the man, as he expressed it, who had "downed" his favorite student in the examination. It seemed that Dr. Billings had received his order to appear for examination so late that when he presented himself there was doubt whether the examining board would consider him at all. The board was disposed to let matters go, as the marks had been made up and all were well satisfied with the results. When it was found that Billings was from Indiana, it was taken for granted that he would not succeed in passing the examination at all, and that his shrift would be a short one. The members of the board thereupon began to examine him, and to their surprise he did so well that they concluded he might get in at the end of the list. In order not to do any injustice to those already marked, they then concluded to give him the same examination which the rest had gone through. At the end of the following day, when he had answered all the questions satisfactorily, they concluded that he would rank so high that it might be necessary to examine him a third day to see how high his marks would be. When the examination was over, he was at the top of the list. This had attracted Letterman's attention. The rusticity of the methods of the army at that time is well shown by the fact that the surgeon-general of the army came with Dr. Letterman to see how the man who had passed such an examination was managing a hospital.

There is an interesting account, in Dr. Garrison's volume, of Dr. Billings' work as a surgeon at the battle of Gettysburg. He had little or no help there, and there were no special arrangements for hospitals. It was difficult indeed for him to provide the

absolute necessities of life for 700 wounded patients. He describes that they were obliged to dig their own latrines and had no shovels. He was compelled to send out to neighboring farms for implements, and after half a day's search, finally got a shovel and I think also one axe. Yet during the few days which followed the battle, Dr. Billings was operating constantly. Indeed he seemed almost the only person who was doing such work in connection with 700 wounded. It is not at all surprising that he shortly afterwards broke down in health.

I shall be glad to have someone who has had a first-hand opportunity of seeing the present war in Europe tell us something about how the sick and wounded are taken care of there.

Dr. T. B. FITCHER: In reference to Dr. Smith's paper, it might be worth while to call the attention of those not familiar with them to the six volumes on the Medical and Surgical History of the War of the Rebellion. I think there are copies in the library here. They give a wonderful account of the war from a medical and surgical aspect, and anyone who looks over the illustrations will be greatly impressed with the care that was used in their preparation. Dr. Osler very frequently referred to the volumes on diseases of the intestinal tract, and in his clinic and at the bedside very frequently had those volumes brought for inspection. The plates on diseases of the intestinal tract, typhoid perforation and dysentery are as good as you will find in any work on diseases of the intestines published up to the present time. Many are reproductions of the excellent specimens in the Army Medical Museum in Washington.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

APRIL 3, 1916.

1. **The Treatment of Emergency Cases of Ectopic Pregnancy.** Dr. E. H. RICHARDSON.
To appear later in the BULLETIN.
2. **Experimental Nerve Repair.** Dr. DEAN LEWIS, Chicago, Ill.
To appear later in the BULLETIN.

APRIL 17, 1916.

1. **Some Recent Investigations on Ductless Glands.** (Abstract.) Dr. W. B. CANNON, Boston, Mass.

During the past four or five years many of the researches of the Harvard Physiological Laboratory have been concerned with the bodily changes which accompany strong emotions, such as fear and rage. These are fundamental experiences in man and the lower animals, so much so that their expression constitutes a sort of common language. The studies which have been carried on have revealed interesting relations between these emotions and certain glands of internal secretion, and have suggested also a way in which emotional excitement may occasion pathological states.

When a cat becomes infuriated, the pupils are dilated and the hair is erect from the neck to the end of the tail. But besides these surface manifestations there are internal changes; for example, the heart beats rapidly and the activities of the stomach and intestines are stopped. Both the internal and the external changes are due to the passage of nerve impulses to viscera along the neurones of the sympathetic division of the autonomic system. The relation of the fibers connecting the central nervous system with these neurones is such as to provide for diffuse action on all the viscera that are innervated by this division.

The adrenal glands are supplied with nerves from the sympathetic division; and also the secretion of the adrenal medulla

affects all structures innervated by the sympathetic division precisely as if they were being stimulated by its impulses. We have found that the adrenal glands secrete adrenin in times of great excitement, that there is an increased liberation of sugar from the liver so that glycosuria may result, that there is an abolition or prompt lessening of muscular fatigue, and that there is a very much more rapid clotting of blood. It is known also that adrenin causes a redistribution of blood in the body so that it is sent, away from the alimentary canal whose activities are inhibited, to the heart, the lungs, the central nervous system and active skeletal muscles. It is known, also, that adrenin causes dilation of the bronchioles and it is known that it increases the number of red blood corpuscles per cubic millimeter, an increase which Lamson has shown occurs also to a marked degree in cases of emotional excitement.

These changes, as true of man as of the lower animals in times of great emotional stress, are significant when the conditions which would give rise to the emotions are considered. Fear is associated with the instinct to flee; rage with the instinct to fight. These are the emotions and instincts underlying the struggle for existence. They are also the emotions and instincts into which all other instincts may be readily turned when they are thwarted. The internal changes are all directed towards increasing the efficacy of the organism for physical struggle. The increased blood sugar provides a source of muscular energy. The altered distribution of blood and the increased number of red blood corpuscles arrange for carrying an abundance of oxygen to active structures. The dilated bronchioles allow ready ventilation of the lungs when oxygen is greatly needed and carbon dioxide is being produced in large amounts. The provision for lessening muscular fatigue is directly useful in muscles likely to be employed in continued action. The rapid coagulation of blood tends to preserve that precious fluid in cases of injury to blood vessels. The organism in which these changes most promptly occur has the greatest re-inforcement of its abilities and is most

likely to be favored in physical struggle. These arrangements for re-inforcement account for the great power and endurance which are exhibited in times of intense excitement.

Other glands than the adrenal are not so readily studied because of the difficulty of recognizing their secretions. It has long been known, however, that physiological activity is accompanied by the presence of an electrical difference which may be observed by connecting an active part with an inactive part of the body through a sensitive galvanometer. Justification of this method of studying glands can be obtained by applying it to the submaxillary gland. It has been found that the electrical change begins before the external secretion appears, disappears as secretion stops, and is not related either to flow of fluid in the ducts or a change of blood flow in the capillaries. Since the only feature that cannot be abolished without abolishing the electrical change is secretion, the electrical effect is a true indicator of a secretory process. When this method, therefore, is applied to the thyroid gland, the positive testimony of the galvanometer is evidence of thyroid secretion.

The electrical method shows that the thyroid gland is subject to impulses from a part of the sympathetic division of the autonomic system, i. e., the cervical sympathetic. The secretion comes promptly—after a latent period of from 5 to 7 seconds. The vagus nerve is without control, and pilocarpine, as a stimulator of vagus endings, is likewise without control. The influence of the sympathetic is not due to anemia, for shutting off the blood supply has no such effect as is produced by sympathetic stimulation.

Control by the sympathetic implies that adrenin may be effective in stimulating the thyroid. This, in fact, is the case, for a marked electrical change is produced when adrenalin (0.1 cc. of 1:100,000) is injected intravenously into a cat. Furthermore, the action current of the thyroid appears if the nerves to the adrenal gland are stimulated, an effect which does not occur if the adrenal glands have been previously removed, and which is delayed if the return of blood from the abdominal cavity is delayed, until the blood is again allowed to flow.

Thus a hormone relation between the adrenal and the thyroid is clearly demonstrated. This electrical evidence, which was obtained in co-operation with Mr. McKeen Cattell, has been confirmed by the observations of Dr. Robert L. Levy. He has found that both stimulation of the cervical sympathetic trunk and injection of stimulating doses of adrenalin greatly augment the effects of small doses of adrenalin in raising blood pressure. This increase of efficacy of adrenalin is not produced if the thyroid glands have previously been removed.

The proof that the thyroid responds rapidly to sympathetic stimulation, and that it is effective in combination with adrenal secretion, shows that there is another bodily change to be added to those already mentioned as occurring in times of great emotional excitement.

In the course of this work two questions have arisen. First, why are organs which are disturbed in times of emotional stress not disturbed at other times? It seemed probably that they were protected from interference by a high neurone threshold interposed between the central nervous system and the visceral cells.

Consequently, only when great excitation is present in the central nervous system is this threshold crossed and the changes in the viscera brought to pass. The second question is, why, in certain pathological cases, is there apparently frequent or continuous disturbance of these same viscera? It seemed possible that this might be due to a wearing down of the high threshold here or there from frequent or great emotional experiences. Thus the situation would be like a break in a dike, and only a slight disturbance in the central nervous system might then be needed to result in a pouring through of impulses at the low point and consequently a fairly frequent or continuous disturbance in the viscera innervated by this region. Thus dyspepsia, tachycardia and probably persistent glycosuria, reported as having an emotional origin, might be accounted for.

To test the effect of continuous stimulation the phrenic nerve was fused with a peripheral portion of the cut cervical sympathetic. This operation, done with the aid of Dr. C. A. L. Binger, resulted in some animals in tachycardia, increased excitability, loose movements of the bowels, exophthalmos on the operated side (in one case) and, as Dr. Reginald Fitz showed, in great increase of metabolism (in one case an increase of 130 per cent). These phenomena have disappeared on removal of the thyroid gland on the operated side. The adrenal glands in two animals that have died of the disease have been greatly enlarged.

The changes thus produced resemble in many respects the symptoms of exophthalmic goitre and support the view that this disease may be primarily due to overactivity of that part of the nervous system disturbed in emotional excitement, possibly, as suggested above, caused by a local stimulation in the cervical region. Two vicious circles may be operative: one through the nervous system due to increased excitability from increased thyroid secretion and resulting thus in increased nervous stimulation of the gland; the other through the blood stream due to increased adrenal activity from overaction of the thyroid and stimulating the thyroid in turn in the manner indicated above.

The evidence previously presented shows that, besides any routine function, the adrenal gland has an emergency function brought out in times of great excitement. It is not unreasonable to suppose that the thyroid gland likewise has an emergency function evoked in critical times, which would serve to increase the speed of metabolism when the rapidity of bodily processes might be of the utmost importance, and, besides that, augmenting the efficiency of the adrenin which would be secreted simultaneously.

2. **The Latent Period in the Growth of Bacteria.** DR. A. M. CHESNEY, New York City.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

APRIL 6, 1916.

1. **History and Discovery of the Secretory Glands.** DR. MORTIMER FRANK, Chicago, Ill.

To appear later in the BULLETIN.

NOTES ON NEW BOOKS.

Hospitals and the Law. By EDWARD VALENTINE MITCHELL, LL. B., College of Law, University of South Dakota, author of "The Doctor in Court." (New York: Rebman and Company, 1915.)

This valuable little book deserves to be in the library of every hospital. It is not a formal treatise on law for the guidance of the trained lawyer, but rather a manual for the hospital administrator, to give him needed instruction upon the rights, privileges and responsibilities of the hospital. From it he will learn that every hospital must be conducted with reasonable skill and dili-

gence under competent medical advice and assistance; that the rights of a charity hospital, established for the public welfare and the relief of suffering differ widely from those of a private sanitarium, established for gain by private parties; that the former, being supported by gifts and endowments for charitable purposes, cannot divert these funds to the payment of damages as long as its governing board exercises proper care in the selection of physicians or nurses; that hospital authorities in the exercise of such care cannot be held responsible for accidents or misadven-

tures, even if their employees have failed to show unusual discretion or skill in the discharge of their duties: it is sufficient if they have acted wisely and to the best of their judgment. The status of the charitable hospital which receives private patients, who pay for their care and treatment, is also the same. The private patient is in a quasi-charitable relation, because he avails himself of the facilities afforded by an institution established as a charity, and the payments which he makes are received to maintain and extend the charitable work of the hospital. The same principle also applies in suits for damages because of careless or wrongful acts of employees, provided that the hospital authorities exercised due care in selecting, procuring and engaging them. This principle has been established as necessary to guard charitable funds from the schemes of blackmailers, adventurers and malingers.

The book also treats of the relations of officials and employees; of the need of adequate records made contemporaneously with the event by physicians and nurses; of the consent of patients prior to an operation; of the consent of friends to an autopsy in non-legal cases.

We are gratified to see a reference to a decision of the court in a Western state, in which it was held that the good faith of a physician in refusing to discharge an unrecovered mental patient because of the latter's irresponsibility was an ample justification for his course, even when the patient had been imperfectly committed.

As has been previously said, the book is worthy of the attention of all hospital officials.

Essentials of Physiology. By F. A. BAINBRIDGE and J. A. MENZIES. Price, \$3.00 net. (London: Longmans, Green and Company, 1914.)

The object of this book, to meet "the requirements of the medical student preparing for a *pass* examination . . .," in the opinion of the reviewer has been very well accomplished. The italics in the quotation are the reviewer's, as he wishes to point out that the book should not be relied on alone by students while *studying* the subject of physiology. There is a complete lack of adequate reference to original sources, and the matter is necessarily presented in too dogmatic fashion to give the student the proper perspective for any effective thinking or successful application of the knowledge imparted.

In brief, to use a term employed in this country, the book is a high-grade "Quiz Compend" without any questions asked.

C. D. S.

Laboratory Methods. By WILLIAMS and WILLIAMS. Third Edition. Price, \$2.50. (St. Louis: C. V. Mosby and Company, Publishers, 1915.)

According to the author's preface note, this book is "especially designed for the general practitioner who desires to make, easily and inexpensively, examinations on which he may depend." The authors have devised a simplification of methods, both as to apparatus and technique, and claim to have given only the best tests, so that the reader will not be perplexed by being obliged to do any choosing. According to an introductory note by Victor C. Vaughan, "this little volume shows how the general practitioner can, at a very small cost, equip a laboratory in which he can do most excellent work." Such a statement is probably a true one, and the idea of encouraging more careful studies of patients is highly to be commended, but in the opinion of the reviewer, the methods he suggests are apt, in the long run, to do much more harm than good. So many inaccuracies could be pointed out, so many misleading short-cuts have been suggested, that it is somewhat difficult to pick out one more glaring than another.

The book is divided into 17 chapters, a number of which bear rather unusual titles, such as "Vascular Dramas," "Diaz versus Widal," "To Find the Treponema in Six Minutes," and so on. Each chapter is introduced with a summary of the apparatus which will be needed for that particular type of work, and this apparatus is pictured on the opposite page. At the end of the book a chapter entitled "Indications for Laboratory Aids" is given, so that it only becomes necessary to turn to it, look up any given disease and promptly find what can be done in the laboratory to clinch the diagnosis. A number of rather interesting suggestions are made in this chapter, such as the searching "of muscle bits for encapsulated larvæ" of *Ascaris lumbricoides*; and that in all cases of diabetes mellitus a search of the stools should be made for intestinal parasites. Under pernicious anæmia one is advised to endeavor "to discover the cause, for which examinations of the urine and feces should be made." On the other hand one finds quite an extensive list of conditions, such as small-pox, measles, yellow fever, sun-stroke, arthritis deformans, epistaxis, diseases of the thyroid, etc., which appear only as titles with no suggestions at all as to how the laboratory can be of use. The puzzled practitioner is set straight in Chapter IX as to the diagnostic value of the diazo reaction, compared with the Widal test, in typhoid fever, but no suggestions are made for blood cultures in this condition. Under the heading "Every Day Stool Tests" it is stated that there is no need for making comparisons of the common ova "when the symptomatology, geographic distribution and other factors are considered." This statement is, of course, a helpful one to anyone endeavoring to rule out helminthiasis.

These few examples, of which hundreds of others could be cited, are enough to indicate in a general way, the scope of this book. It seems a pity that, whereas the authors themselves realize that no book of this size can include all that is good in the medical laboratory, they should perpetrate upon the medical profession a work which tends to encourage the misinterpretation of everyday facts and leaves one utterly stranded when it comes to running down anything unusual.

S. R. M.

Twilight Sleep. By ALFRED M. HELLIMAN, M.D. Price, \$1.50. (New York: Paul B. Hoeber Company, 1915.)

The first half of the book presents a good review of the literature and deals nicely with the controversial side. In the sixth chapter the pros and cons of American opinion on the subject are taken up and from there on is an exposé, especially of the application of the Gauss method. The employment of agents other than scopolamine-narcophine is gone over in the ninth chapter, while the tenth proffers a review, with concluding remarks defining the value of the procedure. An addendum displays specimen charts and the last pages are devoted to a complete bibliography to June, 1915.

W. L. M.

The Adolescent Period: Its Features and Management. By LOUIS STARR, M.D., LL.D., Fellow of the College of Physicians of Philadelphia; Fellow of the Royal Society of Medicine, London, etc. (Philadelphia: P. Blakiston's Son and Company, 1915.)

This little book of about 200 pages is a continuation of a former work, "Hygiene of the Nursery," and its purpose is to present an outline of the physical and psychical changes which are developed between the end of childhood and the close of adolescence.

It presents an excellent introductory chapter on the growth and development of muscle power. It treats of automatisms and explains their connection often with an asymmetrical development of the muscles and their relations to excessive physical inactivity and mental concentration. The remedies for them the author be-

Heves to lie in diversified industrial education, manual training and gymnastics, and plays, games and sports.

The next chapter speaks of athletic training for boys, in which he urges the necessity of a careful preliminary examination as to the competency of the heart, lungs and kidney function to undergo such training. He does not approve of strict athletic training for all boys, because of the bodily hardships and restrictions of diet, which may be injurious to some. All meals should be substantial and not hurried, and plenty of time for sleep is all-essential. The training advocated for girls is less definite, and one gets the impression that athletics are less feasible for them.

The chapter on the disorders of adolescence is one of the most interesting and helpful in the book. It takes a wide range, and in addition to the ordinary bodily diseases more common at this period deals with spinal curvature, abnormalities of speech, sleep anomalies, nervous disturbances such as hysteria, and mental disturbances such as over-conscientiousness, anxiety neuroses, depression, melancholia, neurasthenia and disturbed mentality. The remarks upon the connection of sexual development with these states are very judicious.

The chapter on the faults of adolescence opens the interesting topics of delinquency, truancy, lying, theft, incendiarism, intemperance, prostitution, suicide, etc. In reading it one gets an impression that many of these faults are not so much the outgrowth of the natural development of adolescence as the result of feeble-mindedness or inherent mental defect. Some of them at least do not seem to belong here.

The remaining chapters relate to menstruation and sexual enlightenment. The latter seems to be a fairly successful handling of a very difficult subject. The book is to be commended to thoughtful parents.

Urgent Surgery. By FELIX LEJARS. Translated From the Seventh French Edition by William S. Dickie, F.R.C.S., and Ernest Ward, M.A., M.D., F.R.C.S. Vol. II. The Genito-Urinary Organs—The Rectum and Anus—The Strangulated Hernias—The Extremities. Price, \$7.00. (New York: William Wood and Company, 1915.)

This second volume of Lejars' well-known work contains nearly 600 pages of text, is profusely illustrated, and well indexed. The

translation preserves admirably the lucidity of style of the original done into excellent English. The typographical arrangement, by which subjects, paragraph headings and important words and sentences are emphasized, renders the locating of any desired reference quick and general reading easy.

The subject matter is indicated in general by the sub-title of this particular volume. The various lesions are briefly but clearly described, their etiology is mentioned and a very clear but succinct description of the treatment presented, which is made all the more easy to grasp by the numerous good illustrations. To the captious, there might be some question as to the choice of lesions considered as deserving discussion in a work devoted to urgent surgery. Thus, in the section devoted to the genito-urinary organs, although some ovarian conditions are included, no mention is made of cysts with twisted pedicles, nor is extra-uterine pregnancy taken up; whereas, on the other hand, lacerations of the perineum incident to labor are considered in some detail—a condition no doubt requiring attention, but certainly, in comparison with the other two lesions just mentioned, not to be regarded as urgent. The section devoted to the rectum and anus is very well presented, the methods described are admirable, and the choice of subjects for inclusion is not open to criticism. The portion of the book dealing with strangulated hernia is really a very complete monograph of over 100 pages, including a consideration of even the rare forms of this most important surgical emergency. The last part of the book is concerned with the urgent surgery of the extremities and naturally is largely taken up with a discussion of wounds, fractures and dislocations. Here again the characteristics of clearness, brevity, and good judgment, both in choice of subject-matter and in methods of therapy, are predominant. One is perhaps a little surprised to find the question of bone-planting, that has been so much discussed of recent years, especially in English and American literature, dismissed with scarcely more than bare mention. The author evidently makes much greater use of the older methods of suture and ligature for the fixation of fragments in open operations on the bones.

W. E. D.

BOOKS RECEIVED.

Who is Insane? By Stephen Smith, A.M., M.D., LL.D. 1916. 12°. 285 pages. The Macmillan Company, New York.

An Autobiography. By Edward Livingston Trudeau, M.D. Illustrated. 1916. 8°. 322 pages. Lea & Febiger, Philadelphia and New York.

Transactions of the Clinical Society of the University of Michigan. October, 1914-October, 1915. Volume 6. Edited by the Secretary-Treasurer. 1915. 8°. 133 pages. Ann Arbor, Michigan

A Reference Handbook of the Medical Sciences. Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. First and second editions edited by Albert H. Buck, M.D. Third edition, completely revised and rewritten. Edited by Thomas Lathrop Stedman, A.M., M.D. Complete in eight volumes. Vol. vi. Illustrated by numerous chromolithographs and four hundred and ninety half-tone and wood engravings. 1916. 4°. 967 pages. William Wood and Company, New York.

The Treatment of Acute Infectious Diseases. By Frank Sherman Meara, M.D., Ph.D. 1916. 8°. 540 pages. The Macmillan Company, New York.

The Primary Lung Focus of Tuberculosis in Children. By Anthon Ghon. English edition. Authorized translation by D. Barty King, M.A., M.D. (Edin.), M.R.C.P. (Lond. and Edin.). With seventy-two text illustrations, one black and one colored plate. 1916. 8°. 172 pages. J. & A. Churchill, London.

A Practical Treatise on Infant Feeding and Allied Topics. By Harry Lowenburg, A.M., M.D. Illustrated with 64 text engravings and 30 original full-page plates, 11 of which are in colors. 1916. 8°. 382 pages. F. A. Davis Company, Philadelphia.

Deutsche Frauenheilkunde. Geburtshilfe, Gynäkologie und Nachbargebiete in Einzeldarstellungen. Herausgegeben von E. Opitz. Zweiter Band, *Der abdominale Kaiserschnitt.* von Professor Dr. Otto Küstner. Mit 10 Abbildungen. 1915. 8°. 186 Seiten. J. F. Bergmann, Wiesbaden.

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STUDIES ON THE LOCALIZATION OF CEREBELLAR TUMORS.

V. THE CRANIAL NERVES.

By ERNEST G. GREY, M.D.

(From the Surgical Service of the Peter Bent Brigham Hospital, Harvard Medical School.)

In the previous four papers of this series on localization in the posterior cranial fossa the following topics have been considered: staggering-gait, limb-ataxia, the Romberg test and adiadochocinesis; "the pointing reaction and the caloré test;" posterior new growths without nystagmus;" and the position of the head and suboccipital discomforts." The present report has to do with the significance of cranial nerve involvements. It is based upon an analysis of the records of 63 cases with intra- or extra-cerebellar tumor confirmed either at operation or on post-mortem examination.

As previously stated, the material has been drawn from the records of a series of several hundred patients with syndromes of cerebellar disease in the neurological services of Dr. Cushing at The Johns Hopkins Hospital previous to October, 1912, and at the Peter Bent Brigham Hospital since that date. Most of the cases have been personally observed by the writer.

The surgical treatment of subtentorial new growths now embraces a bilateral approach to the posterior fossa which affords the opportunity to investigate not only the two cere-

bellar hemispheres but also the recess on either side. Notwithstanding this, however, there still remains a small proportion of cases in which the tumors lie anteriorward and are not exposed at the first operation. It is for cases of this type that it seems desirable to secure as much information as is available regarding cranial nerve involvements in order to appraise more correctly their value as localizing guides.

For the purpose of the present analysis subtentorial new growths have been divided into four groups: first, the unilateral cerebellar tumors—those which involve one hemisphere; * second, the median tumors—those which involve the vermis and approximately equal amounts of each lateral lobe; third, the unilateral recess tumors—those which lie in one

* In three patients suffering from unilateral endotheliomata the tumors did not occupy the usual position in the cerebellopontine angle, but lay more posteriorward, embedded in the lateral lobe. They were so characteristically cerebellar tumors, however, that they have been included in this group.

cerebellopontine angle; and fourth, the median extracerebellar tumors which lie inferior to the vermis.

The extent of the cranial nerve involvement is often dependent upon the stage of the disease. The determination as to what period is "early" and what is "late" rests, as Collier has pointed out, upon the severity of the symptoms and the rapidity of growth of the tumor. In the present report the findings fairly well represent an average picture since they include both incipient and advanced cases. They illustrate, furthermore, the range of symptoms exhibited by a series of such individuals when they first appear for surgical treatment.

Many explanations are offered to account for the appearance of contralateral nerve palsies. Thus the N. abducens is sometimes affected indirectly through constriction by the lateral branches of the basilar artery (Cushing²⁰). The cranial nerves on the side opposed to the lesion are occasionally stretched and injured through a displacement of the pons and the medulla from the median line in the direction of the tumor by a dislocated cerebellar lobe, or by pressure on the contralateral side of the pons by the displaced cerebellar lobe (Spiller²¹). In certain instances the nerves opposite the lesion may be injured by pressure against the sharp edge of the dura where they emerge from it (Wernicke²²). More often, probably, such a palsy arises through pressure of the pons and medulla of the opposite side against the base of the skull.

NERVI OLFACTORII.

Historical.—In patients with increased intracranial tension Muskens²³ has determined that disturbances of the olfactory sense are of frequent occurrence. Where large new growths occupied the posterior cranial fossa he found more involvement of the first cranial nerve than was evident with tumors situated elsewhere in the brain. The usual explanation of this is that the dilated third ventricle crowds the structures to either side of it and results in pressure on the nerve. Mingazzini,²⁴ however, has reported a case of cerebellar disease in which he attributed an anosmia on the side contralateral to the tumor to pressure on the pole of the temporal lobe.

Mills²⁵ and others have suggested that in some cases the anosmia may result from nerve-choking similar to that which occurs in choked disc. Collier,²⁶ on the contrary, found that anosmia was not more frequent among his cases with secondary atrophy than among the patients suffering with diseases other than of the nervous system.

Unilateral Cerebellar Tumors (24 cases).—Only 1 patient showed an involvement of the olfactory nerve (complete anosmia) on admission. An advanced choked disc here pointed toward a marked increase in intracranial tension. A second patient detected odors readily but complained of occasional hallucinations of smell. The choked disc here measured about 3 D.

Median Cerebellar Tumors (16 cases).—In this group only 1 showed a definite impairment of the first nerve. The eye-grounds in this instance revealed advanced changes with a considerable disturbance of vision.

Cerebellopontine Tumors (18 cases).—A complete anosmia was found in 2 patients, both of whom had old choked discs. In

one instance secondary atrophic changes had advanced almost to blindness. A third patient, with an optic disc elevation of 5 D., gave the history of disturbances of smell particularly on one side; examination, however, disclosed no appreciable decrease in olfactory discrimination. Smell was very slightly affected in another—choked disc of 5 D.

Median Tumors Inferior to the Cerebellum (3 cases).—None of the patients in this group experienced any appreciable impairment of smell.

Comments.—The sense of smell was definitely impaired during the course of the growth of a subtentorial tumor in 4 of a series of 61 patients. Each of the four patients showed a definite increase of intracranial pressure as determined by the elevation of the optic discs, by Roentgen-ray study of the skull, and by operative findings, namely, increased tension of the cerebellar structures, herniation of the medulla and cerebellum into the spinal canal, etc. Many of those with a normal olfactory sense, however, showed an equally marked rise of intracranial pressure.

In Dr. Cushing's opinion, anosmia is almost always a false localizing sign (Fern-Symptom) and may be due to nerve constriction. In a patient with a large unlocalized endothelioma, who died some months after a palliative operation and who had a complete anosmia, he found that the olfactory nerves were almost completely severed by the interclinoid dural margin. It is possible that this may be a common explanation of the symptom.

Several of the patients in this series gave a history of hallucinations of smell. Undoubtedly these were distant symptoms also due to the secondary internal hydrocephalus.

NERVI OPTICI.

Historical.—It has long been recognized that choked disc is of very frequent occurrence in patients with cerebellar new growths and that, as a rule, it appears early in the course of the disease and rapidly advances to secondary atrophy unless decompressive measures are adopted. Finkelnburg²⁷ however, has recorded four cases of cerebellar tumor, verified by operation, in which choked disc was absent throughout the entire periods of observation. And Mingazzini cites cases of cerebellar new growth, some without appreciable changes in the eye-grounds and others with primary optic atrophy. Growth in the cerebellopontine angle, of course, may exist for years without leading to changes in the fundi.

Unilateral Cerebellar Tumors (25 cases).—Four patients showed increased tortuosity of the veins, hyperemia of the disc, or more or less filling of the cup with edema of the nerve-head, without having any measurable elevation of the latter. A marked swelling of 5 or more D. was evident in 6. In 10 the degree of swelling varied from 1 to 5 D. The remaining 5 on admission showed the picture of secondary optic atrophy with receding discs.

Median Cerebellar Tumors (16 cases).—In 1 merely a slight haziness of the disc margins was observed. There were 6 with secondary atrophy, 6 with advanced elevation of the discs, and 3 with less marked, but nevertheless definite choked disc.

Cerebellopontine Tumors (19 cases).—Every patient in this group had choked disc. Two showed marked changes—over 5 D. swelling. In 4 the degeneration had advanced to secondary atrophy.

Median Tumors Inferior to the Cerebellum (3 cases).—A full-blown choked disc was found in each of the 3 patients.

Comments.—In all but 6 of the 63 patients there was a definite choked disc. The fundi in these six, with one exception, showed changes, most of which we regard as indicative of increased intracranial tension. Minor changes of this nature with very little elevation of the disc, of course, are chiefly significant when the history and repeated ophthalmoscopic study demonstrate that they have appeared since the onset of the trouble.

The tumors in the six cases just referred to were all intracerebellar. Except for one instance (cerebellar tubercles in a patient with an illness of six weeks) the duration of symptoms previous to admission was not appreciably less than that of many of the cases of the same class with definite choked disc.

While recess tumors may exist for years without appreciably affecting the fundi, a swelling of the nerve-head is practically inevitable in the later stages of the disease. It does not occur, however, until there is some obstruction to the cerebrospinal fluid outflow and, consequently, it is an important indication of an existing internal hydrocephalus.

While choked disc in itself has no appreciable localizing significance, since it is not infrequently noted comparatively early in the course of certain supratentorial tumors, it may have some importance in this respect when it is associated with other signs. It is our experience that the early appearance and high degree of changes in the eye-grounds, when they appear in company with some of the so-called cerebellar symptoms, are important confirmatory evidence pointing toward a subtentorial localization of the new growth.

NERVI OCULOMOTORII ET ABDUCENTES.

Historical.—Weakness of the muscles supplied by the third, fourth and sixth nerves in patients with cerebellar tumors is rarely due to a primary involvement of these nerves or their nuclei, but is usually the result of a peripheral involvement, as a rule, of a secondary nature. A nuclear type of paralysis with a paresis of a number of eye muscles of both sides occurs especially in tumors of the vermis where pressure is exerted in the direction of the corpora quadrigemina (Mingazzini).

Mills²⁸ quotes Wernicke as stating that sixth nerve paralysis is most apt to be present as a distant symptom when the tumor is situated in the cerebellum, and he points out that in this respect the sixth nerve differs from the third nerve which is more likely to give distal symptoms with a lesion of the cerebral hemispheres. That the abducens is indirectly paralyzed more often than any other cranial nerve has been emphasized by Collier.

Because of this extreme sensitiveness of the abducens to basalward directed pressure Homburger and Brodnitz²⁹ look upon isolated sixth nerve paresis as an important localizing sign for subtentorial new growths. They do not regard this, however, as evidence pointing toward the side of the lesion, for such a paralysis frequently occurs contralateral to the tumor. Since a paresis of these nerves in cerebellar tumor is

due frequently to an obstructive internal hydrocephalus, it is clear that any pathological process which leads to a primary or secondary hydrocephalus—such as meningitis—may similarly affect the eye muscles. Such cases have been reported by Bramwell³⁰ and others. But lesions of this type are relatively uncommon as compared with cerebellar new growths.

Stewart and Holmes³¹ found that the majority of the patients developed varying degrees of external rectus palsy on the side of the disease—often transitory and liable to recur. As a rule, this was more marked in the patient with extrathalamic than in those with intra-cerebellar tumor. In the latter class of patients both external recti were often affected, though the involvement was always greater on the side of the lesion. This bilateral weakness was met with most frequently in tumors of the vermis compressing the floor of the fourth ventricle.

A weakness or paralysis of the conjugate lateral movements of the eyeballs towards the side of the new growth has been frequently found in patients with subtentorial tumors (Bruns,³² Bruce,³³ Oppenheim,³⁴ Stewart and Holmes,³⁵ and others). When secondary atrophy has led to blindness, the eyes at rest are frequently kept deviated to the side opposite the growth. Mills places paresis of the associated ocular movements in patients of this class among the most common effects of cranial nerve involvement. Such a conjugate deviation, however, is not always toward the side contralateral to the disease, for, as Bruce³³ has pointed out, irritative lesions of Deiters' nucleus may lead to associated ocular movements in the direction of the tumor. At present many hold that such disorders are not manifestations of cerebellar disease, but are due secondarily to unilateral compression of the pons. Disease of the nerves supplying the eye muscles alone almost never causes paralysis of conjugate deviation.

Skew deviation (a downward and inward position of the eye on the side of the lesion and an outward and slightly upward position of the other eye) has been described in cerebellar tumor. It was observed frequently, after acute attacks and after operation, by Stewart and Holmes. Oppenheim³⁴ has encountered it much less often and then almost only after operation.

Nystagmus is generally regarded as one of the most significant symptoms of cerebellar affections. While in such cases it is held to be an expression of disease of either the ear or the central nervous system (Bárány³⁶), it may appear, in cases in which an ocular muscle has been paralyzed but is in process of recovery, if the eyes are directed steadily in a direction which necessitates the active movement of the formerly paralyzed muscle (Stewart³¹). It appears probable that nystagmus of cerebellar origin results from an ataxia of the extrinsic eye muscles (Mills and Weisenburg,³⁷ Wilson and Pike,³⁸ and others). In view of these considerations it seemed best to include certain clinical features of this symptom in the present report on cranial nerve involvements, none of which were touched upon in an earlier paper of this series (Grey³⁹).

According to Stewart and Holmes³¹ and Bruns,³² the character of the jerks has some localizing significance. They regard as typical, slow, deliberate jerking movements to the side

of the lesion on looking in this direction, with a gradual recession of the eyes toward the middle plane. To the opposite side the movements are of smaller range and occur in more rapid succession.

Spontaneous nystagmus with the eyes directed forward is occasionally observed in patients with new growths in the posterior fossa. In direction, according to Bárány,² Wilson and Pike,³⁵ and others, the slow deviation may be away from the side of the lesion though it may be to the sound side, depending on whether we are dealing with an irritative or a destructive lesion. Horsley²⁸ has shown that a careful electrical stimulation of the white matter in the neighborhood of the dentate nucleus or of the body of the dentate nucleus itself, provokes a horizontal nystagmus towards the side excited. This, however, is not the view of Joliat,²⁹ who believes that a localized cerebellar lesion manifests itself by a nystagmus always directed toward the diseased side.

Unilateral Cerebellar Tumors (26 cases).—Eye muscles unaffected: 10 patients—3 with incipient optic changes, 4 with choked disc of 2, 3, 7 and 8 D., respectively, and 3 with secondary atrophy (blind).

History of diplopia but no apparent paresis: 4 patients—3 with advanced choked disc and 1 with secondary atrophy.

Homolateral abducens alone affected: 3 patients—in 1 very slightly (discs hyperemic), in a second definitely (choked disc of 3 D.), and in a third a paralysis (choked disc of 3 to 4 D.).

Contralateral abducens alone affected: 1 patient—choked disc of 3 to 4 D.

Both sixth nerves alone affected: 2 patients—equally involved in 1 (normal eye-grounds), and more homolateral to the lesion in the other (choked disc of 3 to 4 D.).

Oculomotor nerve alone affected: 2 patients—slightly involved homolateral to the disease in 1 (choked disc of 2 to 3 D.), and both weak in the other (early secondary optic atrophy).

Conjugate ocular movements affected: 7 patients—in 1 toward the tumor (blind); in a second toward the side contralateral to the lesion (blind); in a third, to some extent in all directions (choked disc of 3 D.); and in a fourth, good in all directions, but poorly sustained (choked disc of 5½ to 6 D.). Conjugate deviation was only slightly restricted toward the disease in the remaining 3.

Median Cerebellar Tumors (16 cases). Eye muscles unaffected: 4 patients—2 with incipient changes, 1 with choked discs of 1½ and 3 D., and another with secondary atrophy and blindness. History of diplopia but no apparent paresis: 1 patient—choked disc of 2 D.

Unilateral weakness of the abducens alone: 4 patients—in 2, in which one hemisphere was slightly more involved than the other, the paretic muscle was homolateral to the more affected side—choked disc of 7 D. and secondary atrophy respectively. The 2 remaining patients had advanced choked disc.

Both sixth nerves alone affected: 2 patients—choked disc of 6 to 7 D. and secondary atrophy, respectively.

One oculomotor nerve alone affected: 3 patients—all had advanced choked disc.

Unilateral weakness of the abducens and oculomotor nerves: 1 patient—choked disc of 6 to 8 D.

External ophthalmoplegia: 1 patient—choked disc of 6 to 7 D.

Conjugate ocular movements affected: 4 patients—in all there was some restriction to one side (all had advanced choked disc).

Cerebellopontine Tumors (19 cases). Eye muscles unaffected: 6 patients—1 with choked disc of 2 D., 4 with an elevation of 3 to 5 D., and 1 with early atrophy.

History of diplopia but no apparent paresis: 2 patients—choked disc of 1 to 1½ D. and 5 D., respectively.

Homolateral abducens alone affected: 2 patients—choked disc of 3 to 4 D. each.

Oculomotor nerve alone affected: 5 patients—in 2 the homolateral nerve (3½ and 4 D., respectively); in 1 the contralateral nerve (4 to 5 D.); and in 2 both nerves (more on the homolateral side—choked disc of 5 D. and secondary atrophy, respectively).

Abducens and oculomotor each affected: 3 patients—in 2, both homolateral (choked disc of 3 to 4 D. and blind, respectively); and 1, the homolateral sixth and contralateral third nerves.

Conjugate ocular movements affected: 2 patients—in 1, restricted in all directions (5 D.); in the other, restricted toward the lesion (4 to 5 D.).

Median Tumors Inferior to the Cerebellum (3 cases).

Eye muscles unaffected: One patient—choked disc of 5 D.

Both abducens affected: 2 patients—choked disc of 3 to 4 D. in each.

Skew deviation of eyes: Definite in 1 patient before operation.

Conjugate ocular movements affected: 1 patient—restricted in all directions (6 D.).

Nystagmus—Character of the Jerks with the Eyes in the Lateral Positions.

Unilateral Cerebellar Tumors (13 cases with lateral nystagmus):

Jerks slower and coarser with eyes toward the lesion: 8 patients (one doubtful).

Jerks to either side equal in rate and size: 5 patients.

Irregular jerks with eyes toward the lesion (none in other positions): 2 patients.

Irregular jerks with eyes away from the lesion (none in other positions): 2 patients.

Median Cerebellar Tumors (10 cases with lateral nystagmus):

Jerks to either side equal in rate and size: 5 patients (in 3, coarser to one side in other examinations).

Jerks slower and coarser to one side: 5 patients (in 3 with asymmetrically placed tumors the coarser jerks corresponded to the most involved side).

Cerebellopontine Tumors (17 cases with lateral nystagmus):

Jerks coarser and slower with eyes toward the lesion: 8 patients.

Jerks equal in rate and size to either side or variable from day to day: 9 patients.

Medial Tumors Inferior to the Cerebellum (3 cases).

Jerks equal in rate and size to either side: 1 patient.

Jerks variable in character from day to day: 2 patients.

Spontaneous Nystagmus with the Eyes Forward—Its Direction. (Present in 12 of 29 cases with lateral nystagmus examined; the direction was noted in 10).

Unilateral tumors with quick component away from the tumor: 6 patients.

Unilateral tumors with the quick component toward the tumor: 1 patient.

Median tumors with nystagmus to one side: 3 patients.

Comments.—As regards the abducens palsy and the resultant diplopia, it would seem that many of the involvements may be attributed to a strangulation of the nerve by the lateral branches of the basilar artery. Since this type of lesion was first pointed out by Dr. Cushing,¹⁹ numerous corroborative specimens have been obtained in this clinic. To preserve the relationship of the vessels to the nerve which exists *intra vitam*, for post-mortem examination, it is of course essential that the brain be hardened with formalin *in situ* before it is removed.

Since no recognizable relationship has been found to exist between the degree of involvement of the third and sixth cranial nerves and the degree of intracranial pressure, it is probable that such lesions are mainly dependent upon the situation of the new growth below the tentorium and the individual variations in the configuration of the lower surface of the brain and the base of the skull. For the purpose of localizing tumors in one or another part of the posterior cranial fossa, a paresis or a paralysis of these nerves has practically no significance.

In several patients, when the eyes were directed forward, the slightest change in the position of the eyeballs would bring about a reversal in the direction of the nystagmus. In certain others having spontaneous nystagmus with the eyes directed forward, a slight movement to one or the other side of the midline would obliterate the jerks. Fixation—*i. e.*, voluntary effort—as a rule, induced or increased the oscillations of the eyes.

It was pointed out in an earlier report (Grey²³) that there was no discernible relationship between the degree of intracranial pressure and the presence or absence of nystagmus. This finding and the observations recorded above are clinical data in favor of the view held by many that the nystagmus seen in cerebellar disease is very frequently of cerebellar origin—an asynergy of the eye muscles.

In the paper on nystagmus just referred to, it was shown that this symptom may be absent in certain new growths of the vermis and hemispheres. Caloric tests in most of the cases cited demonstrated an absence of any impairment of the fundamental mechanism of labyrinthine nystagmus. When this report was made, it was suggested that the absence of rhythmic movements of the eyes in a patient exhibiting a cerebellar tumor syndrome points toward an intracerebellar localization of the lesion. Since that time only one case has appeared in this clinic which has proven to be an exception to the rule. In this instance there was a fourth ventricle tumor lying inferior and somewhat posterior to the vermis.

An impairment of conjugate deviation of the eyes is frequently encountered in the advanced cases. While this impairment is described as being toward the diseased side, we have seen paralysis of conjugate movements toward the opposite side. Since such a paralysis is thought to be due, in many instances, to lateral pressure upon the pons, a contralateral weakness may be explained in much the same way as are the motor and sensory changes occasionally noted in the homolateral extremities, *i. e.*, by pressure upon the opposite side of the pons.

In the less advanced cases impairments of this nature are much more infrequent. It is with the earlier type of lesion that we have most to do at present, thanks to the more prompt recognition of cerebellar disease by the medical profession, and, accordingly, affections of associated, lateral, ocular movements have no great significance for localizing subtentorial tumors within the posterior fossa.

Skew deviation of the eyes is rarely seen prior to operation in tumors of the posterior cranial fossa.

The rule which states that the nystagmus is slower and coarser with the eyes turned toward the tumor is subject to many exceptions. When, however, there is a definite and persisting difference in the size and rate of the jerks with the eyes in the lateral positions, the nystagmus is usually suggestive of the side of the lesion.

NERVI TRIGEMINI.

Historical.—An impairment of the corneal reflex (Hyporeflexie oder Areflexie der cornea) is regarded by Oppenheim²⁴ as one of the most important features of the symptomatology of unilateral tumor in the posterior fossa. Since the activity of the corneal reflex may be affected by lesions elsewhere in the brain, Redlich²⁵ considers this sign to be of great diagnostic value only when it is found early in the course of the disease before the severe general pressure symptoms and definite nerve palsies appear. Areflexia cornealis has been reported in the eye contralateral to the tumor (Rossbach²⁶).

Irritative symptoms of pressure on the fifth nerve—hyperesthesia, neuralgic pain, etc.—are likewise among the early indications of a tumor encroaching upon the pons. They appear on the side of the new growth (Monakow²⁷) in the skin and mucous membrane innervated by the trigeminus (Cushing²⁸).

Disturbances of taste in the anterior two-thirds of the tongue are here considered under the fifth nerve, though there still remains considerable uncertainty regarding the course of the gustatory fibers beyond the chorda tympani (Quix²⁹). In a study of the effects of trigeminal neurectomy Dr. Cushing²⁸ was led to believe that the fibers did not pass by way of the trigeminus. Mingazzini³⁰ only rarely found taste disturbed in cerebellar tumors.

The sensory division has been found to be more often affected than the motor in both intra- and extra-cerebellar tumors (Stewart and Holmes, Bruns, and Mingazzini).

Where the motor division of one trigeminus is paralyzed, there is a failure of the corresponding masseter and temporalis to contract in chewing, and the jaw can be moved only toward the affected nerve. On opening the mouth the jaw deviates to the affected side.

Unilateral Cerebellar Tumors (25 cases).

Neither trigeminus affected: 12 patients.

Cutaneous sensory disturbances—irritative or paretic: on the side of the lesion, 2 patients; on the side opposite the lesion, 4 patients; on both sides, 2 patients.

Corneal reflex affected: homolateral to the tumor, 1 patient; contralateral, 1 patient; on both sides, 1 patient.

Taste: anterior two-thirds of tongue affected, 4 patients.

Motor division affected: homolateral to the tumor, 2 patients; contralateral, 3 patients.

Median Cerebellar Tumors (16 cases).

Neither trigeminus affected: 3 patients.

Cutaneous sensory disturbances: unilateral, 3 patients (in 1, with a symmetrical growth, homolateral to more affected side).

Corneal reflex affected: unilateral, 2 patients; bilateral, 1 patient.

Taste affected: 2 patients (unilateral).

Motor division affected: unilateral, 2 patients.

Cerebellopontine Tumors (19 cases).

Neither trigeminus affected: 4 patients.

Cutaneous sensory disturbances: homolateral, 10 patients; contralateral, 1 patient; bilateral, 2 patients.

Corneal reflex affected: homolateral, 6 patients; contralateral, 1 patient; bilateral, 3 patients (in 2 more on the side of the lesion).

Taste affected: homolateral, 4 patients; contralateral, 1 patient; bilateral, 2 patients.

Motor division affected: homolateral, 4 patients; contralateral, 1 patient.

Median Tumors Inferior to the Cerebellum (3 cases).

Neither trigeminus affected: 3 patients.

Comments.—From the analysis given above the conclusion may be drawn that, in subtentorial new growths, involvements of the fifth nerve have no topographical importance in diagnosis (within the posterior cranial fossa) unless the tumor lies in the cerebellopontine angle. Such a localization is likely only when the homolateral eighth (or seventh) nerve is also affected.

Clinical and post-mortem observations in this clinic have repeatedly demonstrated that the fifth and seventh nerves may be stretched to a surprising extent by recess tumors, without any serious interference with their function, provided that the new growths are sufficiently slow in their growth to permit accommodation of the nerves to the new conditions. It appears that the eighth nerve is less able to accommodate itself under similar circumstances. The greater frequency of involvement of the auditory nerve as compared with the trigeminus and the facialis, however, is in part explained by the fact that recess tumors grow from the former much oftener than they do from the latter.

In several patients suffering from early recess tumors, who complained of pain in the distribution of the trigeminus without appreciable symptoms of increased intracranial tension, the differentiation from tic douloureux was very difficult for a time. The detection of slight sensory changes on the affected side, of course, led to the correct diagnosis.

The recognition of the cause of this type of trigeminal pain is important, since cases are on record (Weisenburg²³) in which the condition has been mistaken for tic douloureux and been treated by an operation on the Gasserian ganglion.

NERVI FACIALES.

Historical.—A weakness of the seventh nerve similar in origin to the asthenia noted in the homolateral limbs was never encountered by Stewart and Holmes. Mills and Weisenburg, however, have observed not only a unilateral loss of emotional expression but also a loss of all or almost all expression, both of which they attribute to cerebellar disease.

Fibrillary twitchings in the distribution of the seventh nerve and even convulsions which appear to be Jacksonian in character may form conspicuous features of the symptomatology of a recess tumor (Mills,²⁴ Weisenburg²⁵).

Spiller²⁶ has drawn attention to a form of dissociation of facial movement which may be the first sign of weakness of the

facial nerve from pressure of an angle tumor. This consists of a loss of emotional movement of one side of the face with preservation or possible slight impairment only of voluntary movement of the same side. In connection with slight nerve deafness, this may be of localizing value.

The fact has been pointed out by Lasaren²⁷ that the lowest branch alone of the facial may be affected by tumors of the posterior fossa, both for voluntary and emotional movements. Since minor degrees of asymmetry of the face, however, are found not infrequently in normal individuals, it is occasionally difficult to interpret slight differences between the two sides.

As is well known, a lesion of the cortico-nuclear path results in a lower facial palsy of the opposite side. It is accompanied, as a rule, by a paresis or paralysis of the extremities also on the side opposite to the disease. A crossed paralysis (hemiplegia alternans) exists only when the fibers are affected between the place of crossing of the facial paths and the nuclei of the seventh nerves.

When the peripheral nerve is involved, all of the branches are affected and, since the nucleus is the trophic center, electrical examination shows (where the nerve is paralyzed) a reaction of degeneration. In pontine disease the upper facial is frequently spared. The differentiation between lesions which affect the facial nerve in the pons and those which involve it in its peripheral course rests upon the presence of other symptoms which result from the disturbance of neighboring structures by the new growth. A facial palsy which appears on the side opposite to that of a cerebellar tumor is probably due to pressure on the pons (Stewart and Holmes). The seventh nerve (the nerve trunk which arises in the pons from the lower and upper facial nuclei) is purely motor and has no sensory functions (Mills²⁸).

Unilateral Cerebellar Tumors (25 cases).

Neither facial nerve affected: 17 patients.

Homolateral facial nerve affected: 5 patients—3 in both upper and lower divisions; 2 in lower division alone.

Contralateral facial nerve affected: 1 patient.

Questionable involvement of facial nerve: 2 patients—in 1, homolateral; and in the other, contralateral.

Median Cerebellar Tumors (16 cases).

Neither facial nerve affected: 13 patients.

One facial nerve affected: 2 patients—in upper and lower divisions in both.

Questionable involvement of one facial nerve: 1 patient—lower division only.

Cerebellopontine Tumors (19 cases).

Neither facial nerve affected: 6 patients.

Homolateral facial nerve affected: 8 patients—in 4 the weakness was discernible in the lower division only.

Questionable involvement of one facial nerve: 5 patients—homolateral in 1; and contralateral in 4.

Median Tumors Inferior to the Cerebellum (3 cases).

Neither facial nerve affected: 3 patients.

Comments.—The results of the clinical observations on involvements of the seventh cranial nerve indicate that a paresis of one facialis in subtentorial tumor is strong presumptive evidence of the side of the lesion, though it appears not infrequently in median growths. A questionable involvement of the seventh nerve, on the other hand, is deceptive in this re-

spect. due probably to the relative frequency of normal facial asymmetries of slight degree.

Mills and Weisenburg have recorded two cases of cerebello-pontine tumor with convulsions of the facial muscles which appeared to be Jacksonian in character. A similar case, in this clinic at the present writing, deserves to be reported. A man of 34 years with a left recess endothelioma showed, besides the usual signs of increased intracranial pressure, a very slight motor and sensory involvement of the fifth nerve and a more marked affection of the eighth on this side, but no weakness of either seventh nerve. The muscles in the whole distribution of the homolateral facialis, however, showed frequent clonic spasms lasting one-half to two or three minutes. There was no trigeminal pain. In addition to the cranial nerve disorders, there was a slight disturbance of sensation in the leg of the same side, together with a definite weakness and a measurable atrophy of the thigh muscles; and tests for coordination elicited asynergic movements, particularly in the limbs homolateral to the spasms. The patient was bedridden, but careful questioning made it seem very probable that he had had a staggering, drunken gait previous to the appearance of the unilateral sensory and motor disturbances.

The facial convulsions of Jacksonian character coupled with the sensory and motor changes all in the same half of the body strongly suggested [a cerebral lesion with] cortical irritation. The presence of a new growth in the parietal lobe, however, could not account satisfactorily for the involvement of the fifth, seventh and eighth nerves and for the ataxia of the limbs and the staggering gait. Since all of these symptoms could be explained by assuming a tumor to be present in the left cerebello-pontine angle, a suboccipital exploration was carried out, exposing the lesion.

When such spasms of the facial muscles are encountered, it is important to differentiate them from true Jacksonian convulsions, as they may easily be ascribed to cortical irritation.

NERVI ACUSTICI.

Historical.—After the second nerve Mingazzini found the eighth to be the most frequently affected cranial nerve in patients with cerebellar tumor. An impairment may be due to direct pressure on the nerve, to an infiltration of the trunk, to a tumor of the nerve sheath, or finally, perhaps, to pressure on the medulla or pons.

Extracerebellar as contrasted with intracerebellar growths are chiefly responsible for the symptoms arising from disturbances of the cochlea and labyrinth—impaired hearing, tinnitus, dizziness, impaired equilibrium, nystagmus, and tremor of the head. A unilateral or a bilateral deafness, when it appears for the first time as part of a brain tumor syndrome, is found almost exclusively in patients with tumors arising from the sheath of the acoustic nerve. Collier's experience, it should be mentioned, directly negatives the theory that auditory neuritis, in any way comparable with optic neuritis, occurs in intracranial tumors.

Tinnitus, as encountered by Stewart and Holmes, is of fairly frequent occurrence in recess tumors and is referred always to

the corresponding ear. In tumors which involve the hemispheres it rarely forms a prominent symptom, and when present is vague in character and is not referred to either ear.

Vertigo, according to these observers, is one of the most constant symptoms of cerebellar new growths. In vermis tumors it appears early and endures over a long period (Bruns). This is readily explained by the intimate relations which exist between the vermis and Deiters' nuclei.

It is defined by Wilson and Pike³⁸ as the confusion resulting from the coming into consciousness of afferent impulses concerned with equilibrium which ordinarily are associated (integrated), but now for some reason have become dissociated. While vertigo, strictly speaking, is not a cranial nerve symptom, the ear is the most important of the peripheral organs which send such impulses afferentward, and any slight disturbance of the labyrinth results in a confusion of the patient's conception of his position in space. Moreover, pressure on the eighth nerve has been shown experimentally to be an important factor in the production of vertigo. In view of these facts and since such disorders of equilibrium were not discussed in a recent report on cerebellar coordination (Grey³⁹), an analysis of this symptom has been included in this paper.

In both the intra- and the extra-cerebellar tumors, Stewart and Holmes have found that there is frequently a sense of displacement of external objects in front of the patient from the side of the lesion toward the opposite side. A subjective rotation of self, also frequently present, is always from the side of the lesion toward the healthy side in intracerebellar tumors, but from the healthy side toward the side of the lesion in extracerebellar tumors. Others, however, have failed to have this experience (Bruns, Oppenheim,⁴⁰ Weisenburg, Wilson and Pike³⁸). Wilson and Pike have emphasized how difficult it is to get a distinct history of subjective sensations even from intelligent patients. In a case of Souques⁴¹ with a recess tumor the subjective rotation was in a direction opposite to the rule mentioned above.

The disturbances of hearing and equilibrium recorded in the following analysis appeared for the first time in each case during the course of the illness which necessitated hospital admission.

Unilateral Cerebellar Tumors (24 cases).

Hearing affected in neither ear: 14 patients.

Hearing slightly impaired in homolateral ear: 7 patients.

Hearing greatly impaired in homolateral ear: 2 patients.

Hearing impaired in both ears: 1 patient—more homolateral.

Tinnitus present—not referred to either: 4 patients.

Tinnitus referred to homolateral ear: 4 patients.

Tinnitus referred to contralateral ear: 4 patients.

Median Cerebellar Tumors (16 cases).

Hearing affected in neither ear: 13 patients.

Hearing slightly impaired: 2 patients—unilateral in one; bilateral in the other.

Hearing greatly impaired: 1 patient—unilateral.

Tinnitus present—not referred to either ear: 4 patients.

Tinnitus referred to one ear: 2 patients.

Cerebellopontine Tumors (19 cases).

Hearing affected in neither ear: 3 patients.

Hearing greatly impaired in homolateral ear: 15 patients—in 1 the contralateral ear was also affected.

Hearing slightly impaired in homolateral ear: 1 patient.
 Tinnitus present—referred to both ears: 1 patient.
 Tinnitus referred to homolateral ear: 8 patients.
 Tinnitus referred to contralateral ear: 3 patients.

Median Tumors Inferior to the Cerebellum (3 cases).

Hearing affected in neither ear: 2 patients.
 Hearing slightly impaired in one ear: 1 patient.
 Tinnitus referred to one ear: 1 patient.

Vertigo.

Unilateral Cerebellar Tumors. A careful study of vertigo was made in 13 patients with unilateral new growths. Of this number, 2 had never experienced any definite vertigo, 10 had suffered from it to a moderate degree, and 1 had been greatly troubled by it. With one exception no history of a displacement of external objects or of a subjective rotation of self could be elicited. The exception complained of the objects in his environment moving back and forth when he felt dizzy.

Median Cerebellar Tumors. Vertigo was studied in 10 patients of this group. Three had experienced very little if any real dizziness; 5 had been troubled with occasional vertigo, especially on changing from one position to another; and 2 had suffered much from it. Only one patient experienced any subjective displacement of external objects—the objects moved back and forth. There was no subjective rotation of self.

Cerebellopontine Tumors. Vertigo was studied in 13 patients with recess growths. Every one was found to have experienced some degree of dizziness. In 8 it was not a very troublesome symptom. In the remaining 5, however, it occasioned great annoyance. Two of the latter frequently suffered from a sense of displacement of external objects and a subjective rotation of self. In both the direction of the subjective rotation of self followed the rule laid down by Stewart and Holmes. But only one adhered to the rule pertaining to the movement of external objects. The second patient saw the objects move from the well toward the diseased side.

Median Tumors Inferior to the Cerebellum. Only one patient experienced any appreciable amount of vertigo. It consisted of a sinking feeling and frequently a subjective rotation of self from the healthy toward the diseased side.

Comments.—The observations recorded above indicate that in subtentorial new growths a unilateral impairment of hearing, which appears for the first time in company with general pressure symptoms, is indicative either of a homolateral tumor or, less frequently, of a median growth. When hearing, under similar circumstances, is greatly impaired or lost in one ear, it points toward a homolateral, extracerebellar localization of the tumor. Such a diagnosis is confirmed when either the fifth or the seventh nerve of the same side is also affected.

Tinnitus, it appears, is not a reliable guide to the site of a tumor situated below the tentorium. Even in recess growths it occasionally appears in the unaffected ear—as a rule, at some time subsequent to the perception of the noises on the diseased side. In such instances, particularly when the patient's memory is more or less hazy, the symptom may lead to erroneous conclusions.

Although vertigo is a prominent symptom of subtentorial tumors as compared with growths situated elsewhere in the brain, it has no appreciable significance, in the experience of this clinic, in localizing the disease in one or another part of the posterior cranial fossa.

For the purposes of neurological diagnosis we have found the Bárány caloric test to be of the greatest service in detecting

impairments of hearing due to pressure on the auditory nerve. When a preliminary examination has ruled out any serious disorder of the meatus and the middle ear, this test furnishes a convenient and satisfactory method of gauging air conduction. Less reliance is placed upon bone conduction. While a shortened bone perception (positive Rinné) coupled with great deafness for speech indicates an affection of the auditory nerve, the perception of after-tones and the transmission of tones of the fork to the opposite ear interfere with the Rinné test. It occasionally happens that in patients with recess tumors, even of large size, the tones perceived by transmission in the unaffected ear are referred in part to the diseased side.

NERVI VAGI ET GLOSSOPHARYNGEI.

Historical.—Although cerebellar tumors, cerebellopontine growths in particular, may lie very close to the brain stem without leading to symptoms of bulbar involvement (von Monakow³⁷), they not infrequently exert pressure on the medulla and give rise to disturbances of deglutition, of speech, and occasionally of the circulation and respiration.

The act of swallowing is carried out through the coordination of a system of buccal, pharyngeal, and oesophageal muscles. It is a reflex act, the afferent paths of which arise in the mucous membrane of the pharynx and oesophagus, including branches of the trigeminus, the glossopharyngeus and the vagus. The motor fibers concerned in the reflex arise from the V, IX, X, XI and XII cranial nerves. At the present time the deglutition reflex is thought to be controlled by a definite nervous mechanism, the final motor cells of which are scattered in the several motor nuclei of the afferent nerves just mentioned (Howell³⁸).

While at least five motor nerves participate in the act of swallowing, a peripheral palsy of the IX or X cranial nerve, nevertheless, leads to some disturbance of deglutition. Extracranial disease of the vagus alone, however, as a rule leads to only a slight interference with swallowing. It is often impossible to determine to what extent dysphagia and dysarthria are due to an involvement of certain cranial nerves and to what extent to an involvement of the medulla. In cerebellar disease it seems probable that disturbances of mastication and deglutition at times arise through an incoordination of the involved musculature (Babinsky,³ Rothmann, Mills and Weisenburg and others). According to André-Thomas,⁴ the symptoms following the destruction of the cerebellum are, above all, disturbances of motility, whether the movement be reflex, automatic or voluntary.

Since speech depends upon an associative action of the respiratory, laryngeal, palatal and lip muscles, a dysarthria may result from the involvement of any of the nerves supplying these parts. According to Gutzmann,³⁹ the paralysis of one XII nerve leads to but a slight dysarthria. A bilateral paralysis, however, even incomplete, results in a marked disturbance of speech. Practically no interference with speech accompanies a paralysis of the motor division of the V nerve. The pronounced effects of an inactive facial nerve are well known—an interference with the labial sounds. Where the X nerve is

affected, the usual disturbances of phonation appear, due to the loss of innervation of the vocal cords. Such a paralysis (unilateral) leads not only to a laryngeal paralysis, but also to an involvement of the soft palate so that it does not move with speech.

The disorder commonly associated with cerebellar disease is described as being slurring and drawling, and at times scanning, jerky or a little explosive. This Babinsky and Tournay explain on the basis of hypermetria, adiadiokinesis and asynergy. Mills and Weisenburg believe in a true cerebellar dysarthria. Others, however, look upon such dysarthrias as chiefly bulbar in origin (Gutzmann). Bonhoeffer⁴ and Meige²² regard the drawling character of the speech encountered in cerebellar affections as due to a prolongation of the muscular contractions.

As Weisenburg²² has pointed out, it is not generally recognized that the sensory distribution of the fifth and ninth nerves intermingle. It is presumable that irritation of either cranial nerve will cause pain to some extent in the distribution of the other.

Unilateral Cerebellar Tumors (25 cases).

Speech and deglutition normal (in history and on examination): 14 patients.

Deglutition alone affected (slight): 5 patients.

Speech alone affected (slight): 1 patient.

Deglutition and speech both affected (slight): 5 patients.

Median Cerebellar Tumors (16 cases).

Speech and deglutition normal: 15 patients.

Speech affected (marked): 1 patient.

Unilateral Cerebellopontine Angle Tumors (19 cases).

Speech and deglutition normal: 12 patients.

Speech affected: 7 patients—slight in 3 and marked in 4.

Deglutition affected: 4 patients—slight in 2 and marked in 2 (both of whom had marked dysarthria).

Median Tumors Inferior to the Cerebellum (3 cases).

Speech and deglutition normal: 3 patients.

Comments.—Dysarthria and dysphagia are two of the most striking symptoms of subtentorial new growths. They may appear both in patients with cerebellar lesions and also in those with tumors situated in the cerebellopontine angle. They are usually associated with considerable deformity of the medulla and pons. In the series reported here, these symptoms were encountered a little more frequently with recess growths. It seems likely that without surgical intervention all cerebellopontine tumors would ultimately lead to disturbances of deglutition and speech.

Though dysarthria and dysphagia are occasionally encountered in patients with supratentorial new growths we have come to regard them as very characteristic of intra- and extra-cerebellar tumors.

Nine in the series of patients reported here died with symptoms pointing toward respiratory failure. Here the compensatory changes in arterial pressure, which have been shown by Dr. Cushing²³ to act as a protective mechanism in such cases, were insufficient to counteract the effects of the marked cerebral compression. This probably led to the early depression of the respiratory center. (Horsley and Dixon and

Halliburton.²⁴) The two most recent of these had been disturbed for several weeks previous to the exitus with slight difficulty in speaking, and for a number of days with some disturbances of deglutition. From these cases it appeared likely that the presence of dysarthria and dysphagia might prove to be of service as warnings of an impending respiratory embarrassment. Among the nine patients just cited, however, there were only three who had been disturbed with symptoms of this nature. In one there was no especial difficulty in swallowing, but speech was much affected. The other two were the recent cases mentioned above. Since six of the fatal cases had neither deglutition nor speech disturbances, and in view of the fact that 16 of the 19 patients that showed one or the other of these symptoms did not succumb to a respiratory failure, it is apparent that these features have no great significance as forerunners of a medullary paralysis, provided that decompressive measures are adopted within a reasonable time. When they are very marked, however, Dr. Cushing believes that they make surgical intervention hazardous. He has found that both may be greatly increased by manipulation and efforts to remove the tumor.

The dysarthria noted here was mostly of the thick, slurring, drawing type.

NERVI ACCESSORII.

Historical.—Paralysis of the spinal accessory, a purely motor nerve, causes a complete paralysis of the sternocleidomastoid muscle, and a partial or very infrequently a total paralysis of the trapezius. Usually this is readily detected. Cerebellar new growths rarely lead to an involvement of the nerve.

In unilateral cerebellar disease a diminution of power is occasionally noted in the limbs on the side of the lesion. In the absence of sensory disturbances and atrophy it is thought by many to be due to the loss of the cerebellar control of the affected part (Luciani,²⁵ André-Thomas, Hunt,²⁶ Mills, and others). This asthenia is found in the distal and proximal muscles of the homolateral extremities and in the homolateral trunk muscles. A similar weakness of the muscles innervated by the spinal-accessory nerve, so far as can be ascertained, has never been reported.

Unilateral Cerebellar Tumors (25 cases).

Neither spinal accessory affected: 22 patients.

Homolateral muscles weak: 2 patients.

Questionable homolateral weakness: 1 patient.

Median Cerebellar Tumors (16 cases).

Neither spinal accessory affected: 16 patients.

Cerebellopontine Tumors (19 cases).

Neither spinal accessory affected: 18 patients.

Homolateral muscles weak: 1 patient.

Median Tumors Inferior to the Cerebellum (3 cases).

Neither spinal accessory affected: 3 patients.

Comments. In the 63 cases reported here, a weakness of the muscles innervated by the spinal accessory nerve was found in but 3. In each instance there was only a moderate loss of strength and this was homolateral to the lesion.

In operating on tumors in the cerebellopontine angle we have frequently noted a twitching of the homolateral shoulder—an observation which points to the close proximity of the eleventh nerve to recess growths. A marked paresis or paralysis of the muscles innervated by this nerve in subtentorial tumors, however, is very rare in our experience. Dr. Cushing has seen only one such case.

NERVE HYPOGLOSSI.

Historical.—When the XII nerve is affected in its intracerebral course (paths from the cortex to the nucleus in the medulla), as is almost invariably the rule in hemiplegia, the tongue is protruded toward the paralyzed side, *i. e.*, toward the side opposite to the lesion in the internal capsule or cortex (Beever⁴). No atrophy of the tongue appears. A paralysis of the peripheral nerve, however, results both in a paralysis and in an atrophy of the homolateral half of the tongue. It is only rarely that a weakness of the muscles innervated by the ansa hypoglossi is recognized. The peripheral twelfth conveys no form of sensation to the tongue (Maloney and Kennedy²⁰).

True bulbar paralysis, as a rule, affects the roots of both hypoglossal nerves. This at first leads to a diffuse bilateral weakness of the intrinsic muscles, together with fibrillary twitchings, salivation and atrophy. During the early course of such a lesion the movements of the tongue are mostly preserved, but they are greatly slowed (Flesch²¹). A double hypoglossal affection of this type materially affects chewing and swallowing, and is rarely seen in cerebellar tumors.

When one-half of the tongue is paralyzed from an affection of the nucleus, root or nerve, there is an inability to touch the teeth and the gums or to protrude the tongue into the cheek of the paralyzed side, while there is perfect freedom of movement to the sound side, the tongue being easily protruded into the cheek of this side and the teeth and gums being readily touched. In advanced cases secondary atrophic changes in the paralyzed half may greatly interfere with the movements of the sound half (Mussen²²). When the tongue is protruded, it deviates toward the side of the paralyzed nerve. An incomplete paralysis, however, may fail to cause any deviation of the tongue (Dinkler²³).

In patients with cerebellar new growths, then, the tongue may deviate toward the normal or toward the diseased side depending on whether the new growth leads to pressure on the pons above the decussation (weakness of the contralateral limbs), or to an involvement of the peripheral nerve or its nucleus. Henschen²⁴ has reported a few cases of recess tumor with crossed paralysis.

Weisenburg²⁵ has reported a case of cerebellopontine tumor in which there were involuntary movements of the tongue. He believes that these spasms were unquestionably the result of irritation of the roots of the twelfth nerve.

Unilateral Cerebellar Tumors (25 cases).

Neither hypoglossal affected: 19 patients.

Homolateral hypoglossal weakness: 2 patients.

Contralateral hypoglossal weakness: 4 patients—a very slight disturbance in 2.

Median Cerebellar Tumors (16 cases).

Neither hypoglossal affected (16 cases).

Cerebellopontine Tumors (19 cases).

Neither hypoglossal affected: 14 patients.

Homolateral hypoglossal weakness: 2 patients.

Contralateral hypoglossal weakness: 3 patients—a very slight disturbance in 2.

Median Tumors Inferior to the Cerebellum (3 cases).

Neither hypoglossal affected: 3 patients.

Comments.—The muscles innervated by the hypoglossal nerves were found affected on one or the other side in 11 of the 63 cases. While the homolateral half of the tongue was weak in four, the contralateral half appeared to be affected in seven. It is important to note, however, that of the seven cases with muscular weakness on the side opposite the lesion, four showed only a very slight involvement. Minor differences of this sort might perhaps be explained in much the same way as are the corresponding normal asymmetries of the facial muscles.

From these observations it is evident that a weakness of the muscles innervated by one twelfth nerve is of very little significance for localizing tumors in one or another part of the posterior cranial fossa. A peripheral paralysis (involvement of the nucleus or nerve) accompanied by symptoms of increased intracranial pressure, of course, points toward a subtentorial localization of the growth.

In our experience an atrophy of the lingual muscles is rarely met with in cerebellar tumors.

SUMMARY AND CONCLUSIONS.

Since anosmia in cases with intracranial tumor is usually a distant symptom due to a secondary internal hydrocephalus, it has no appreciable significance for the localization of the new growths. Uncinate gyrus symptoms may appear, secondary to an internal hydrocephalus. The sense of smell was affected in about seven per cent of the 63 certified cases analyzed in this report.

While choked disc in itself has no appreciable localizing significance, since it is not infrequently noted comparatively early in the course of certain supratentorial tumors, it may have some importance in this respect when it is associated with other signs. It is our experience that the early appearance and high degree of changes in the eye-grounds, when they appear in company with some of the so-called cerebellar symptoms, are important confirmatory evidence pointing toward a subtentorial localization of the new growth.

Very little reliance can be placed on an involvement of the third or sixth cranial nerve as a guide to the side occupied by the new growth, in the localization of tumors in one or another part of the posterior fossa.

The observations recorded here are in favor of the view held by many that the nystagmus seen in cerebellar disease is very frequently of cerebellar origin—an asynergy of the eye muscles. The rule which states that the nystagmus is slower and coarser with the eyes turned toward the tumor is subject to many exceptions. When, however, there is a definite and

persisting difference in the size and rate of the jerks with the eyes in the lateral positions, the nystagmus is usually suggestive of the side of the lesion.

Since impairments of conjugate deviation of the eyes are only infrequently encountered in the less advanced cases of subtentorial tumor, they have relatively little importance for the localization of tumors within the posterior cranial fossa. Skew deviation of the eyes in cerebellar new growths is rarely seen prior to operation.

In subtentorial tumors involvements of the fifth cranial nerve have no topographical importance in diagnosis (within the posterior fossa), unless the tumor lies in one or the other cerebellopontine angle. Such a localization is likely only when the homolateral eighth (or seventh) nerve is also affected.

A paresis or a paralysis of one facial nerve in tumors of the posterior cranial fossa is strong presumptive evidence of the side of the lesion, though a paresis appears not infrequently in median growths. When the eighth (or the fifth) nerve of the same side is also affected, the diagnosis of a homolateral growth may be made. A questionable involvement of the seventh nerve, on the other hand, is deceptive in this respect due, probably, to the relative frequency of normal facial asymmetries of slight degree.

In subtentorial new growths a slight unilateral impairment of hearing, which has appeared for the first time in company with general pressure symptoms, is indicative either of a homolateral tumor or, less frequently, of a median growth. When hearing, under similar circumstances, is greatly impaired or lost in one ear, it points toward a homolateral extra-cerebellar localization of the tumor. Such a diagnosis is confirmed when either the seventh or the fifth nerve of the same side is also affected.

Tinnitus, it appears, is not a reliable guide to the side occupied by a tumor situated below the tentorium.

Although vertigo is a prominent symptom of subtentorial tumors as compared with growths situated elsewhere in the brain, it has no appreciable significance for the localization of the disease in one or another part of the posterior fossa.

The presence of dysarthria and dysphagia (unless they are very marked) in patients with subtentorial tumors, though a source of anxiety, is no contra-indication to operation, since neither is a reliable sign of an impending respiratory paralysis. When they occur, they constitute two of the most striking symptoms of intra- and extra-cerebellar new growths.

The spinal accessory nerve is only rarely involved (in less than five per cent) in tumors of the posterior cranial fossa. When this nerve is affected, the muscular weakness is not marked and it is homolateral to the growth.

A weakness of the muscles innervated by one twelfth nerve is of very little significance for the localization of tumors in one or another part of the posterior fossa.

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TREATMENT OF THE EMERGENCY CASES OF ECTOPIC PREGNANCY.

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Thirty-five years ago extrauterine pregnancy was considered a surgical rarity, only an occasional case being observed even in the largest obstetric institutions of the world. Lawson Tait is credited with having been the first to perform a laparotomy for a ruptured tubal pregnancy in 1883. Since then, our knowledge of this grave anomaly has been magnificently enriched both through its steadily increasing incidence and through the voluminous literature which its widespread study has produced.

So far from being a rare affection to-day, there can scarcely be found a general hospital of any size in the larger cities which is unable to report a dozen or more cases annually. The reason for this increased frequency is not altogether clear, although the suggestion that it may be explained through the spread and prevalence of gonorrhoea has much to support it.

A great deal of speculation has been indulged in concerning the etiology of ectopic pregnancy. The various theories advanced from time to time have one characteristic in common, namely, the fundamental idea of a mechanical factor, which suffices to arrest the fertilized ovum during its downward progress through the tube. A considerable variety of conditions has been definitely shown to thus operate in individual cases. These may be conveniently classified under three heads:

1. Conditions which obstruct the lumen of the tube.
2. Congenital and acquired abnormalities of the tubal wall.
3. Conditions arising outside the tube by which its lumen is narrowed or obliterated.

Most of the conditions thus grouped represent isolated observations and are relatively rare. By far the most common specific cause of tubal pregnancy is the so-called "follicular salpingitis." As the name indicates, this is an inflammatory process in which the folds of tubal mucosa become oedematous and their free margins extensively adherent to each other in such a way as to form numerous little blind pouches or follicles in which a fertilized ovum may lodge. Indeed, this change may be so extensive as to give a reticulated appearance to a cross-section of the tube. While the absolute proof is lacking, one can scarcely resist the conclusion from the available evidence that this condition is brought about through gonorrhœal infection of the tubes. If the necessary proof is supplied through later work, it will thus be shown that the overwhelming majority of cases of ectopic pregnancy are caused by gonorrhœa.

Once the fertilized ovum becomes arrested in the tube from any cause whatsoever and begins to develop, it becomes a serious menace to the life of the individual.

A number of eventualities are possible both as regards the fœtus and the mother. We are concerned here, however, only with that large group of cases which terminate acutely either by tubal abortion or rupture prior to the eighth week of development, and are associated with an alarming degree of hemorrhage. These constitute the grave emergency cases which require the exercise of the nicest surgical judgment for their proper handling. The clinical picture is so typical that the diagnosis does not often present serious difficulties. The usual

story is that the individual prior to the onset of the attack was enjoying perfect health, oftentimes not even having experienced the early symptoms of pregnancy; that, while engaged in some commonplace activity, she was suddenly seized with a lancinating pain of agonizing severity in the right or left ovarian region, which promptly incapacitated her, and was rapidly followed by collapse. When seen an hour or two later by the physician, the condition of the patient is usually such as to excite grave apprehension. If she is conscious, the expression is anxious; the face and mucous membranes present a death-like pallor; there is either restlessness, associated with orthopnea and air-hunger, or absolute quiet with complete relaxation of the voluntary muscles, and shallow, hurried breathing; the pulse is rapid and thready, and the blood-pressure subnormal; the skin is cold and clammy, and the temperature is often subnormal; abdominal tenderness and rigidity are marked, as a rule; and shifting dullness in the flanks is usually demonstrable.

With such a picture pelvic examination is unnecessary, and is apt to do positive harm by loosening a blood clot and exciting fresh bleeding.

The surgical problem in these cases is that of dealing with an acute, intra-abdominal hemorrhage in a patient partly exsanguinated and in a state of profound shock.

Gynecologists are not yet fully agreed as to the best method of dealing with this problem. Indeed, there still exist no less than three distinct schools, each advocating a method of treatment fundamentally different from the other two.

First, there is the radical school, whose teaching and practice are based upon the theory that, given a bleeding vessel in the pelvis, the indications are to clamp or ligate it at the earliest possible moment, irrespective of the patient's condition. They evidently do not believe in polytherapy, but prefer to concentrate their efforts with precipitate haste upon controlling the supposedly bleeding vessels. They, therefore, ignore for the time being the shock already existing, and through their ill-timed operative manipulations succeed handsomely in producing a far graver degree of shock, to the treatment of which, let us hope, they propose later to address themselves, provided the patient survives. As a matter of fact, the death of the patient relieves them of this necessity in from 40 to 50 per cent of the cases thus treated. Fortunately, this teaching is now subscribed to by a small and constantly diminishing number of operators.

Secondly, there is the school of ultra-conservatives, whose most conspicuous representative is Dr. Hunter Robb, formerly of Cleveland, Ohio. In 1908 he reported to the American Gynecological Society the results of a most interesting series of experiments, showing, among other things, that he had been unable to kill a dog by opening the abdomen, dividing bilaterally both the uterine and ovarian vessels, and then promptly closing the incision. When, however, after a half hour or so, he reopened the abdomen of an animal thus treated, and added operative manipulations to the shock already produced by the hemorrhage, the animal invariably succumbed.

Even more striking, perhaps, is his later report of 35 cases of tubal pregnancy treated by deferred operation. In five of these death seemed imminent on admission to the hospital. Not one of the patients was subjected to operation earlier than 18 hours after admission, and some were permitted to wait 12 days, the average time for the entire series being 5 days. Only one death occurred in the series, and this cannot justly be charged to the deferring of the operation.

This report naturally made a profound impression upon the minds of gynecologists the country over. Shortly after its publication, while serving my apprenticeship in the Gynecological Department of The Johns Hopkins Hospital, I had an opportunity of observing a patient treated as Dr. Robb recommends, the results of which led me to promptly reject his plan.

This patient, a robust woman in the prime of life, was admitted in the late afternoon to the private ward in a state of profound collapse from a tubal pregnancy that had terminated acutely a short time before. It was perfectly obvious that any operative procedure would certainly end her life. Accordingly operation was deferred, the measures advocated by Dr. Robb to combat the shock in these cases being promptly instituted, and with the most gratifying results. The improvement was almost immediate and continued throughout the night to such a degree that on the following morning she was considered practically out of immediate danger. The abdomen, however, soon began to distend, and within a few hours meteorism was the dominating feature of the clinical picture. She first suffered from hiccough; then, as the ileus gradually advanced, nausea and vomiting set in, together with a rapidly increasing pulse rate. Every possible measure to overcome the distention was employed by the gynecologist in charge of her, but without avail, so that about 48 hours after admission he was compelled to resort to laparotomy. The improvement following the operation was slight and only temporary, the patient dying two days later of intestinal obstruction.

The consensus of opinion of all who saw this patient was that had laparotomy been done and the large quantity of blood been evacuated from the abdomen as soon as the patient recovered from the initial shock, paralytic ileus would probably not have developed and her life might have been saved.

Probably similar experiences are responsible for the fact that few gynecologists can be found who subscribe to the deferred operative plan of the ultra-conservative school in the management of these cases.

Thirdly, there is the progressive school, which includes a substantial majority of the leading gynecologists of to-day. They believe neither in the precipitate haste of the radicals, nor in the dangerous delay of the ultra-conservatives, but, having appropriated valuable lessons from the experiences of each, they have incorporated them into a rational plan of treatment, which leaves little to be desired.

In this plan all therapeutic effort is first employed to combat the shock. It consists of the use of morphine hypodermically; the subcutaneous or intravenous administration of normal salt solution; when required, the employment of specific

cardio-vascular and respiratory stimulants; elevation of the foot of the bed; bandaging the extremities; and the application of heat externally. As soon as the improvement, which is almost sure to follow, has occurred, as indicated particularly by a slowing of the pulse rate, a substantial increase in pulse volume and blood pressure, immediate laparotomy with evacuation of the blood and removal of the affected tube is indicated. The operation need consume only 15 minutes, and the patient's condition will almost invariably be found better at the end than at the beginning of surgical intervention. I have employed this plan of treatment in nine of these grave emergency cases, and in all except one the results were eminently satisfactory, the convalescence and complete restoration to health being rapid and entirely uneventful in each instance.

The one exception was a case seen on January 19, 1916, in consultation with Dr. S. A. Dodds, of Walbrook, Md. This patient was a white married woman, 31 years of age. She had passed through two normal pregnancies, labors and puerperia, giving birth to two healthy children, aged respectively 7 and 6 years. Four years before she had had an abortion, followed by puerperal fever, and later by some minor gynecological operation—probably a curetment. During recent months the menstrual periods had been slightly irregular, one being 10 days overdue at the onset of this attack. Otherwise she was enjoying perfect health. About 10 a. m., immediately after defecation, she was seized with a pain in the right ovarian region of such violence that she sank to the floor and fainted. A little later, when Dr. Dodds arrived, he found her already in a state of partial collapse and, recognizing the nature of her trouble, he promptly instituted protective and supporting measures of treatment. She gradually responded to these sufficiently well to be removed to the Union Protestant Infirmary, where I saw her at 1.30 p. m. Her condition then was of such gravity as to preclude absolutely any immediate operation. I therefore at once resorted to the therapeutic measures detailed above, which had hitherto in my experience invariably rallied such patients sufficiently to enable them to withstand operation. To these she responded very promptly, but it was a disappointingly feeble response, so much so that at no time during the afternoon did her condition become such as to warrant surgical intervention. Towards the late afternoon she began to lose ground again very slowly, but quite definitely. I then determined to resort to a transfusion of blood as a preparatory measure for the laparotomy.

The necessary arrangements were promptly made and a direct transfusion was done by Dr. B. M. Bernheim.

The improvement in the patient's condition was almost instantaneous and truly remarkable, so that after the donor's blood had been allowed to flow over for only a few seconds, Dr. Griffith Davis considered her condition good enough to administer the ether, the transfusion being temporarily halted.

I then quickly opened the abdomen, evacuated a large amount of fluid and clotted blood, released extensive pelvic adhesions, lifted the uterus forward from extreme retro-displacement, and removed the right tube, which had ruptured near its middle. The right round ligament was then quickly

sutured to the fundus in such a way as to both cover the raw surface at the cornu, and at the same time hold the uterus forward. The incision was closed without drainage, the entire operation having consumed less than 15 minutes.

While the incision was being closed Dr. Bernheim resumed the transfusion, allowing the blood to flow over until the patient had a good pulse and a striking improvement in the color of her face and mucous membranes.

She was returned to her room with a pulse of 108, and her convalescence from then on was entirely smooth and uneventful. She was discharged from the hospital on February 5, only 17 days from the time of her admission.

I have reported this case in detail for two reasons: First, because in a survey of the literature which has appeared since the transfusion of blood was revived and satisfactorily developed, I have been able to find reports of only 16 cases of extrauterine pregnancy in which it was employed. Only six of these cases are reported in sufficient detail to determine the time relation of the transfusion to the laparotomy, and in none of these was it employed, as in my case, immediately prior to operating, for the specific purpose of converting a hopeless surgical risk into one of comparative safety. And, secondly, because it conclusively proves that in those exceptional cases where the usual methods of treatment fail we have in the transfusion of blood a possible life-saving measure.

I therefore unhesitatingly recommend that the necessary preparations for transfusion of blood be made as a routine in these cases, so that it may be promptly resorted to when the usual therapeutic measures fail.

DISCUSSION.

DR. BERNHEIM: I hesitate to enter this discussion as to whether diagnosis in these conditions is simple or not, since I see but few of such cases. But in my experience, which is that of one engaged in transfusion work, death from acute hemorrhage is not at all uncommon, although in the majority of cases there has been a time when supportive measures might have been instituted, that is, by the giving of blood. The patient referred to by Dr. Finney, which the chairman saw, a number of others had also seen. The case occurred at least five or six years ago and was the second transfusion to which I had been called. As Dr. Finney says, the diagnosis had not been made, although it was felt that there had been an intra-abdominal hemorrhage. It was decided to operate on this patient and ascertain the source of hemorrhage, stop the bleeding and then to transfuse. As I have said, it was the beginning of my transfusion work and I really did not know what was best to do in that particular case. So I occupied myself in trying to find a donor, the patient having no relatives or friends at the Union Protestant Infirmary. We found a man who was a cardiac case. He was about to be bled the next day because of his high blood pressure, which was around 180 mm. of mercury, and he readily agreed to give his blood. The patient's abdomen was hurriedly opened and the condition found to be one of extrauterine pregnancy. All manipulations were carried out with great rapidity and wonderful skill, but in spite of this a still further shock was caused. After closure of the abdomen we started to do the proposed transfusion. The method was much more complicated than it is to-day and when, after a good deal of labor and considerable time, we finally succeeded in getting the union, we were so pleased at having successfully accomplished it that we simply stood back and allowed the blood to flow over for about five minutes, at the

end of which time the patient was dead. The pressure of the donor's blood had over-distended the right side of the patient's heart, and since she was unconscious and we were inexperienced at transfusion work, we failed to recognize the signs of this condition, which are now so readily apparent to all engaged in transfusion work.

As I say, that case taught us a good deal: first, that all cases of extrauterine pregnancy are not so easy to diagnose, and secondly, that there is terrific danger in transfusion work in distending the right side of the heart, because of tremendous pressure on one side and almost negative pressure on the other side. In addition, it taught me that in cases of acute hæmorrhage, where operative interference is proposed, the time to transfuse is prior to and during the operation. That is, the patient must be brought out of shock first, before the anesthetic is given and before the slightest manipulation is started. Acting on that basis, we have done many other cases, not only of extrauterine pregnancy, but of other conditions where there has been acute hæmorrhage. In fact, the custom has developed that transfusion is started with the patient on the table and every preparation made for anesthesia and incision. With everything in readiness, the blood is sent over for about two or three minutes, during which time the patient is apparently resuscitated. When such a state of affairs takes place, the patient is anesthetized and the transfusion is stopped, because to raise the pressure in conditions of acute bleeding is simply to pump in and pump out at the same time. After the abdomen has been opened and the bleeding point caught, the transfusion is resumed, by which means the patient can readily be put into such shape that a normal convalescence may be confidently expected.

DR. CULLEN: I should like to differ slightly with Dr. Finney in regard to the question of the diagnosis in cases of tubal pregnancy. While in some cases the diagnosis is difficult or impossible, the clinical picture in the majority of the cases is perfectly evident. On referring to the clinical histories one finds that many of the patients have had a period of sterility extending over several years. Then they have missed one or two periods and have then noticed a slight continuous bleeding. Other patients have had a

very short menstrual flow followed by a faint but constant uterine bleeding. Such a history instantly makes one suspicious of an extrauterine pregnancy. The only other condition that, as a rule, gives such a clinical picture is a chronic pelvic inflammation.

Several years ago I reported in THE JOHNS HOPKINS HOSPITAL BULLETIN eight cases that had been observed in the course of a few weeks. In five of these the diagnosis had been made before the tube ruptured. We impress upon the students continually the importance of diagnosing these cases before rupture occurs. Fortunately in the vast majority of the cases the prodromal symptoms exist weeks before rupture occurs. In a few, however, these are absent, and in such cases the sudden pain in the right or left lower abdomen accompanied by pallor and collapse is the first intimation of the extrauterine pregnancy.

In those cases where tubal pregnancy is suspected, but where doubt exists, the patient should be etherized and a careful pelvic examination made. If doubt still exists, then the uterus should be curetted and the mucosa examined. In the early months of tubal pregnancy there is a sympathetic development of decidua in the uterine mucosa.

Accordingly, the finding of an intact mucosa with, at the same time, a transformation of the stroma cells into decidua, will clearly indicate the presence of a tubal pregnancy.

Several years ago Dr. G. Brown Miller of Washington saw a patient who had been sterile for years. This patient gave a history of missing one period; shortly after this there was a slight but continuous uterine bleeding. He examined the patient under ether, but could detect no abnormality in either Fallopian tube. He curetted the uterus and on examination of the mucosa we found an intact surface epithelium and a stroma consisting of typical decidua. Tubal pregnancy was diagnosed and the abdomen opened. The tubal pregnancy was scarcely 1 cm. in diameter and was unruptured.

I believe the time will come when nearly all cases of tubal pregnancy will be diagnosed before rupture occurs—at a time when the tube can be removed with little or no risk. In those cases where alarming internal hemorrhage has taken place, we must be prepared to transfuse before or during the operation.

THE ETIOLOGY OF DISEASES OF THE CIRCULATORY SYSTEM.¹

ABSTRACT.

By T. C. JANEWAY, M.D.

This study of the diseases of the circulatory system, viewed from the standpoint of their etiology, was undertaken in the endeavor to determine whether there exists at the moment sufficient exact knowledge of the ultimate and of the contributory causes of any of the diseases of the circulatory system, to warrant the efforts which public health officials and life insurance companies are urging to reduce their prevalence. The diseases were considered in the following etiological categories:

1. Known bacterial infections:

- (a) Bacterial or septic endocarditis.
- (b) Other bacterial infections of the circulatory system.

2. Probable, but unproved, bacterial infections:

- (a) The rheumatic infections.
- (b) Benign endocarditis of other origins.
- (c) Acute infectious myocarditis.
- (d) Acute arteritis and phlebitis.

3. Syphilis:

- (a) Of the aorta.
- (b) Of the heart.
- (c) Of the smaller arteries.

4. Rare infections.

5. Parasites and tumors.

6. Intoxications:

- (a) Exogenous.
- (b) Endogenous.

7. Nutritional disturbances.

8. Mechanical disorders.

¹ The Shattuck Lecture delivered before the Massachusetts Medical Society, June 6, 1916.

9. Nervous disorders.
10. Defects of development.
11. Hereditary disease.

The study of syphilis was based upon an analysis of 2,576 admissions to the Medical Service of The Johns Hopkins Hospital, September 21, 1914, to April 2, 1916, showing that of the individuals admitted 85.1 per cent were white, 14.9 per cent were colored. Of these patients, 8.8 per cent of the white and 37.6 per cent of the colored had a positive Wassermann reaction. Of the white 1.6 per cent, and of the colored 17.4 per cent had syphilis of the aorta, while 2.4 per cent of the white, and only 2.1 per cent of the colored had chronic endocarditis. A special study of the possible influence of syphilis in the causation of hypertension showed that, of 320 patients with hypertension during this period, 3.2 per cent of the white and 31.4 per cent of the colored had a positive Wassermann reaction, lower figures than for the incidence of the reaction in all patients of each race. When the patients with evident syphilitic lesions of the aorta or central nervous system, in addition to hypertension, were deducted, there remained only the following insignificant percentages in which a positive Wassermann reaction was associated with no evident clinical manifestations except the hypertension:

Hypertension with renal involvement:

White.	Colored.
0	13.5 per cent.

Hypertension without evident renal involvement:

White.	Colored.
0.9 per cent.	3.1 per cent.

These figures lend no support to the view recently advanced by Stoll that family hypertensive cardiovascular disease is familial cardiovascular syphilis.

The influence of alcohol and of tobacco was studied in the author's series of private hypertensive patients; no convincing proof was obtained.

The relation of diabetes and gout to chronic nephritis and arteriosclerosis was similarly studied statistically; the incidence of past acute nephritis was found to be very small except for pregnancy nephritis in women. The etiological factors entering into the production of arteriosclerosis were also discussed.

Finally, the relative importance of the various causes of myocardial insufficiency was studied from an analysis of the 250 patients of the Hospital showing myocardial insufficiency during the above-mentioned period. The results were as follows:

One-third of our myocardial failures are associated with hypertension. As another large group of these patients die of apoplexy, hypertensive cardiovascular disease assumes first place as a cause of circulatory death. Chronic endocarditis stands next, with syphilis of the aorta just behind, each accounting for about one-sixth of the failing hearts. If we could add the deaths due to syphilis of the cerebral arteries, and to ruptured aneurysms, the position of syphilis and of the other infections would be reversed. The clinically primary myocardial insufficiencies, a motley group etiologically, but largely arteriosclerotic, follow with about an eighth of the blame. Emphysema and its congeners are not far behind, then true bacterial endocarditis, then thyroid intoxication, and various minor causes.

The following practical conclusions were drawn:

- I. Reduction of the mortality from circulatory diseases is attainable.
- II. The measures now possible, which will yield definite results, are, in the order of their importance and feasibility:
 1. The diminution of syphilitic infection and the early diagnosis and intensive treatment of primary syphilis.
 2. The further reduction in preventable infectious diseases, especially diphtheria, scarlet fever and typhoid fever.
 3. The education of the public to consider "rheumatism" a serious disease, particularly in childhood, and to seek competent medical advice at once; and the education of the medical profession to treat even the mildest rheumatic fever in bed with large doses of salicylates from the earliest possible moment.
 4. The provision of convalescent hospitals for the necessarily protracted after care of cases of acute inflammatory disease of the heart and of patients recovering from myocardial insufficiency.
 5. The development of suitable employments for cardiac patients, and of the social and economic machinery necessary for placing them in such employments.
 6. General hygienic measures, including the promotion of temperance.
 7. The medical examination of the supposedly healthy at stated intervals.
- III. No large reduction of the mortality from circulatory diseases is likely until two groups of problems have been solved:
 1. The ultimate causes of hypertension and of chronic nephritis.
 2. The infectious agent of rheumatic fever and its portal of entry.
- IV. The solution of these problems, if of such a nature as to lead to practical measures, with elimination of syphilis, would almost abolish disease of the circulatory system, except in the aged.

The need of the moment, therefore, is for more knowledge; not more knowledge of the dangers of circulatory diseases for the public, which means propaganda, but more knowledge of their causes for the physician, which means ceaseless investigation.

JOHNS HOPKINS HOSPITAL BULLETIN.

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ON SOME OF PROFESSOR LEXER'S WORK AT THE RED CROSS AUXILIARY NAVAL HOSPITAL, VEDDEL-HAMBURG, GERMANY, 1914-1915.*

By MEDICAL DIRECTOR HENRY G. BEYER, U. S. N.

In venturing to speak to you to-day of some of the surgical work done by Prof. Lexer at the *Red Cross Auxiliary Naval Hospital* at Hamburg during the first eight months of the present European war, I would like to have it understood that I am impelled to do so from motives of a pupil's admiration for his master's work and that I have no intention of arrogating to myself the slightest credit in the work itself. My part is merely that of a propagandist and interpreter for which my association with him as his assistant has peculiarly fitted me. With the kind permission of Professor Halsted I would like to discuss with you the special subject of the "Operative Union of Fractured Bones, or Osteogenesis," to the literature of which Lexer, recently, has made important contributions and from which I shall draw freely.¹

Indications.—The operative union of bony fragments is not called for in every form of fracture. Whenever the surgeon succeeds in securing an accurate coaptation of the bony fragments, in fresh fractures, especially of the tibia and femur, nothing besides a well-fitting plaster-of-Paris dressing will be required. The operative union of fractures of the shafts of long bones is indicated: in transverse fractures, in multiple fractures with intervening soft parts between the fragments, in cases in which two neighboring bones would form an unnatural union and where bony protuberances with important and powerful muscular attachments (olecranon, patella, calcaneus, trochanter major) have been torn off. There is at present no military hospital in Europe in which a very large percentage of time is not given up to the treatment of just such fractures.

Time.—Lexer advises waiting at least one week after the injury before attempting the operation. It is his opinion that the periosteum, as well as the soft parts surrounding the injury to the bone, must be given time to recuperate before they can be expected to take their full share in the production of the necessary callus.

The chief considerations in favor of an early operation are: (1) that the periosteum, torn from the surface of the bones, is more easily distinguished than after it has become embedded in thick and firm cicatricial tissue; (2) that the margins of the bony fragments can be more accurately fitted into one another; (3) that the early removal of bloody accumulations relieves the pressure upon the tissues, encourages the restoration of a normal circulation and nutrition in them and, at the same time, prevents the undue formation of adhesions between

the soft parts, all of which would tend to a slow and imperfect formation of callus.

In all gunshot injuries it is safest to wait for the end of cicatrization, as the best granulating surfaces and the smallest granulating points still harbor infectious germs, seriously interfering with the process of healing. Imperfectly healed granulations, therefore, forbid the operation.

Bony Splints Preferred.—A firm and enduring position of the fragments of a long bone is best secured through splints placed either inside the marrow cavities or, externally, upon the surfaces of the shafts of the fragments. As material for internal splints (Bolzen) Lexer has for many years employed pieces of long bones freshly removed from either the same patient (autoplasty) or freshly amputated limbs (homoplasty) and prefers such material to any other, while admitting the usefulness of ivory, steel, silver and magnesium splints under certain circumstances. He uses the splints of a size sufficient to completely fill the marrow cavities and drives them, first, into one of the fragments with a few strokes of a hammer, and then, under extension, counter-extension and extreme flexion, slips the projecting end of the splint into the prepared marrow cavity of the other, finally pushing the margins of the fractured ends into the closest possible contact. In case the marrow cavity of a long bone should be found filled with callus, it is to be hollowed out by means of a sharp chisel. Boring it out electrically is to be avoided on account of the heat, thus produced, injuring the substance of the bone.

Even for purposes of external splinting Lexer prefers living bones to all other forms of splints. He says: "The union of bony fragments by means of living bone is for me the ideal to be pursued in all operative measures on fractures of the long bones, internally as well as externally. Freshly transplanted pieces of bone form an easy attachment to the surrounding soft parts and their blood vessels, thus promoting, instead of retarding, the formation of callus. Just as the external bony splints unite organically with the periosteal callus, just so do the internal bony splints (Bolzen) unite with the myelogenic callus." Another and not the least important advantage in the method of using living bone depends upon the fact that it can be used to replace lost bone, thus practically excluding shortening.

Disadvantages of Foreign Material.—Foreign material must first become encapsulated before organic union can take place with the bone. The development of callus and its transformation into bony tissue is consequently retarded, or even altogether prevented. These disadvantages may not become so apparent where foreign material is used for intramedullary splinting, because the periosteal callus grows over the fractured portion and unites the ends of the fragments. But even

* Address made at The Johns Hopkins Hospital, May 17, 1916.

¹ Lexer, "Blutige Vereinigung von Knochenbrüchen." Deutsche Zeitschrift f. Chirurgie, Band 133. Kriegschirurg. Mitteilungen aus dem Völkerrkriege, 1914-15.

here Lexer has reported frequent failures, occasioned by post-operative myelitis, induced by the presence of these foreign bodies. In cases in which metal, ivory, horn, or boiled bone from cadavers, was used, suppuration as late as a year after operation has been known to occur and compel the removal of the offending substance. These disadvantages are, according to Lexer, eliminated when living bones are used as internal or external splints. Subsequent suppuration in such cases is due, in his opinion, to faulty technique and not to the splints employed.

Important Relation of Soft Parts to Periosteum.—Lexer considers it a very serious error to separate the soft parts from the ends of the fragments in the wound and from the periosteum adherent to the already formed callus covering the bone. Such a procedure damages the reproductive functions of the periosteum very greatly, as may be seen at once when its blood supply is taken into consideration: The diaphysis of a long bone receives its blood supply through the nutrient artery. The metaphysis and epiphysis receive theirs from the vascular networks of their respective joint-capsules, while the periosteum depends for its blood supply exclusively upon the soft parts immediately surrounding it. That portion of the blood supply which comes to the periosteum from the bone-marrow through anastomoses in the cortical substance is diminutive, when compared with that received from its connections with the soft parts immediately covering it on the outside. All reproductive power of the periosteum as, also, that of the endosteum, depends upon new formation of blood vessels.

Quoting from Lexer: "If we produce, subcutaneously, fractures in animals and, later, at intervals (1-6 weeks), inject into the blood vessels a turpentine-mercuric iodine emulsion, so as to render these visible in the roentgenogram, it will be easy to observe a gradually increasing new formation of blood vessels, not only near the seat of the fracture, but also in the neighboring portions of the fractured bone. This new formation of blood vessels becomes noticeable about one week after the fracture and continues to increase well into the fourth week of callus formation, but then gradually subsides. This newly formed blood-vascular supply takes its origin in the periosteal network of capillaries and *not* in that of the nutrient artery. This artery is torn and therefore may cooperate, though very slightly at first, through anastomoses with the periosteal network of vessels and, later, through the production of new vessels of its own. Callus formation having come to an end, all the vessels resume their normal appearance, so that at the end of the sixth week scarcely a difference is noted between the fractured and its corresponding uninjured bone."

For Lexer it has become a firmly established fact that the bone's share in the process of the repair of a broken bone is contributed by the periosteum, through its increased blood-vascular growth greatly assisting in the formation of callus and, thus, of new bone. Hence it follows that during all operations for the union of fractures the periosteum must, first, never be separated from its connection with the soft parts while the fragments are being exposed, and, secondly, laceration of the periosteum itself must be guarded against. These

same principles underlie the formation of the sequestrum after an osteomyelitis. Here the nutrient vessels have become thrombotic or have been partly destroyed in the suppurative process. The periosteum remaining adherent to the soft parts, wherever its vessels have survived, there also promptly begins the formation of the sequestrum.

In gunshot injuries received at close range, where even undeformed bullets produce an explosive effect, large tracts of periosteum remain adherent to the surrounding soft parts, a fact of great significance and to be taken advantage of in bone transplantations. Even the largest defect, an entire diaphysis or section of skullbone, may be replaced by bones of any sort or source, whether it be living periosteal or dead bone, whether of autoplasmic or of homoplasmic origin; even foreign substances, as ivory, metal or horn, may thus be used with perfect clinical success, *as long as the periosteum in the wound remains intact and in connection with the soft parts.*

Moreover, whenever we are confronted with the problem of having to replace a large bony defect we shall be successful only when the freshly obtained, periosteum-covered bone-transplant finds rapid contact with the surrounding soft parts, that is, when placed in such a position that primary agglutination can occur. If this organic fusion fails to materialize, being prevented by hæmorrhage or inflammatory exudates, the transplant is doomed to die and can never be expected to replace the lost bone. The first and foremost function of the periosteum, adherent to the transplant, is that it facilitates a close attachment to the soft parts. Its specific callus-forming function follows as a secondary event in the process of repair. Freshly obtained transplants from the same subject, covered with uninjured periosteum, give the best results.

Causes of Failures.—What constitutes the chief cause of a break of a transplant, whether placed internally or externally, at the seat of the fracture? Always an erosion of the transplant by granulations that destroy the cortical substance after the disappearance of the periosteum. Connective tissue, rich in blood vessels, always appears in those places in which blood has accumulated between the transplants and the soft parts surrounding them; where, in other words, the close contact between the two has failed to occur. With intramedullary splints this sometimes happens where the ends of the fragments have not been freshened sufficiently or where a too prominently projecting tooth has interfered with the accurate coaptation of them. A dead space is thus left, exposing the transplant between the two ends of the fractured bone. This space is first filled with blood and afterwards with connective tissue, the destructive activity of which progresses *more rapidly* than the reparative, callus-forming activity of the periosteum.

Exactly identical conditions would be met with in cases in which transplants are used for the purpose of replacing defects in long bones to prevent shortening, as well as to assure a firm position of the fragments, were it not for the fact that in all such cases transplants, protected by their own periosteum, are here used. All that remains to be done here is to provide such

conditions as will assure the close contact between the soft parts and the periosteal surface of the bone-transplant.

The Operation.—A deep incision is made down to the bone. The soft parts, including all the cicatricial tissues and periosteum, are gently pushed aside. The bared ends of the fragments are lifted out of the wound, the walls of the wound cavity are then carefully freed from the cicatricial tissue, care being taken to avoid as far as possible any injury to the periosteum. The latter is easily recognized by the presence in it of thin layers of callus or by its color alone, which differs somewhat from the whitish appearance of the cicatricial connective tissue. When this procedure is carried out, large tracts of living periosteum remain in vital connection with the soft parts, on the one hand, while the removal of the cicatrices from the walls of the wound facilitates the new formation of blood vessels between it and the bony surface on the other.

Source of Splints.—In all operations for the union of broken bones, by means of living bone transplants, the source of the transplants is of paramount importance. For short splints, pieces of rib from the same patient, the outer sides of which have retained their periosteal covering, are the simplest material that can be employed. Longer splints had better be taken from the periosteum-covered spine of the tibia: A long, slightly convex, incision is made through the skin on the outer side of the spine of the tibia; the tibialis anticus is gently pushed aside outwardly, until the external surface of the tibia lies everywhere and to the extent of about 2 cm., freely exposed. After the periosteum on both sides of the spine has been incised and the desired length and breadth of the future transplant has been marked out, a narrow groove is cut along the whole line of the periosteal incision into the cortical portion of the tibia by means of a fine V-shaped chisel. This circumscribed plate of bone is then easily chipped off by inserting the sharp end of a wide, flat, thin chisel into this groove and driving it in with a few light strokes of a hammer at different places as well as at both extreme ends of the line of the incision, until the plate separates from the underlying bone. Even long plates do not splinter when broad and rather thin chisels are used that are sharp on both sides. Electrical saws must be avoided.

The plate of bone thus removed is at once wrapped up in sterile gauze soaked in warm normal salt solution and kept until used.

In fractures of the long bones in which the transplants are to serve not only the purpose of securing a firm position between the fragments but also that of replacing lost sections of bone, Lexer does not recommend the employment of external splints, notwithstanding the fact that he has used these successfully on the lower jaw. For intramedullary splints (Bolzen) Lexer employs homoplastic material, when available, of the thickness of the entire fibula, ulna, radius or long stria of the femur or humerus, occasionally also metacarpal and metatarsal bones. As autoplasmic material the fibula alone comes into consideration whenever the "Bolzen" are to serve exclusively for giving the fragments a firm position and, consequently, need not be covered by periosteum. The regener-

ation of the fibula begins after the third or fourth week of its removal from the sleeve of periosteum left in the wound cavity.

Points Deserving Special Attention.—Esmarch's bandage should never be employed, since the hemorrhage in the wound must be most carefully controlled by the ligation of all bleeding vessels in order that the wound may be closed perfectly and tampons and drainage tubes avoided. Broad hooks covered with sterile gauze will prevent injury to the tissues. Incisions over bones lying directly under the skin must be curvilinear, so that the skin-cicatrix shall remain free from connection with the bone. Whenever it becomes necessary to proceed cautiously and to have regard for important anatomical structures, before making incisions down to the bone, the tissues are divided layer after layer. Such a procedure is called for in the arm on account of the radial nerve, in the forearm on account of both the tendons and nerves. After thus reaching the last layer of connective tissue over the periosteum the knife is carried down to the bone through both. In the case of a fractured femur that is covered with a very thick musculature, smooth wounds are very desirable. Here the knife is made to enter on the outer side of the thigh and pushed straight through until its point touches the bone. The tissues are slowly divided, the point resting steadily on the surface of the fragments. The knife, having reached the seat of fracture, sinks in deeper, passing on to the second fragment. The periosteum, as well as any possible callus, having been divided throughout, a broad elevatorium is introduced and both are pushed aside.

The free end of the fragments appearing at the bottom of the deep wound are now seized with strong bone forceps and slowly drawn out, while strong flexion is maintained between the fragments to assist in this act. In fresh cases the bloody coagula collected behind the fragments are pressed out of the wound. In the older cases the still adhering periosteum and masses of callus are pushed off from them, so that they may remain at the bottom of the wound and retain their connection with the soft parts unimpaired.

The next step is to search the surfaces of the wound for old cicatrices. These are found mostly over places where the periosteum has been destroyed or where torn pieces of muscular tissue have covered the bony stumps. Such tissue has a whitish appearance and bleeds but little. Finally adhering bony splinters had better be left, providing they exert no noticeable pressure on important nerves and do not tend to produce bony union between two neighboring bones. Even projectiles or portions of them may be left undisturbed when their removal would be attended by injury to the periosteal vessels.

The next step in the operation consists in the preparation of the stumps. In transverse fractures it is usually considered sufficient to saw off a thin disc. In irregular oblique fractures, where tooth-like projections are desirable for dovetailing the ends of the fragments into one another, a fine sculptor's chisel best serves the purpose of freshening the stump. The marrow cavities must be cleared out so as to make the splint fit snugly. At this stage of the operation the fragments are replaced to the bottom of the wound, bleeding vessels are ligated, the cavity is packed with hot salt-compresses to arrest and to absorb

the results of capillary oozing. An examination of the condition of the fracture having, moreover, resulted in giving the necessary information as to what sort of a splint is needed, whether it is to be covered by periosteum or not, the required transplant is sought and introduced into the prepared marrow cavities of the stump. Supposing this to be a fracture of the femur, the splints being taken from the fibula, being about 10 cm. long, the first half is driven into that fragment which was broken off transversely, or nearly so. The end of the splint projecting from this fragment can, naturally, not be introduced into the other by extension and counter-extension alone. We must, in addition, make use of strong flexion ad axin and pull the stumps apart by means of strong bone forceps before we shall succeed in slipping it into the marrow cavity of the remaining fragment.

In fractures of the leg and forearm in which but one bone has been fractured, flexion is, of course, out of the question. In such cases it becomes necessary to chisel out a narrow piece from the second fragment in order to enable the operator to place the projecting end of the bolt into its cavity. In all such cases wiring is also necessary.

The Closure of the Wound.—Suturing of the soft parts begins close over the bone with fine catgut. Periosteum must lie snugly over the bone and all around it. On the femur, from 4-6 such sutures, one over the other, are necessary. If muscles, tendons and nerves have been displaced during the operation they are returned to their normal position after the first peri-

osteal suture has been completed and kept there by sutures, if necessary. In this manner, muscles, fascia and fatty tissues are united with continuous catgut suture, and, lastly, the skin with silk.

After the skin has been cleansed with peroxide of hydrogen, silver leaf is spread over the suture and its immediate neighboring skin surface, according to the method of Halsted (on which method Lexer made a special report in the "Zentralblatt f. Chir.," Nr. 14). A fenestrated plaster-of-Paris dressing is used for the leg, a pasteboard splint for the arm. These dressings remain undisturbed for at least three weeks, providing all goes well, the fragments show perfect coaptation and the limb is in the correct position.

Finally, and in order to complete this account, a few words must be added with regard to the preparation of the field of operation. Lexer rejects the employment of tincture of iodine in every aseptic operation. He says: "Useful as may be the painting with tincture of iodine in emergency cases and in suppurative cases, it accustoms the entire personelle to merely superficial cleanliness, a cleanliness that is insufficient for all operations in which absolute aseptic conditions must prevail. In wounded who have little or no opportunity for bathing for weeks or months, over places where the hardened and dried epithelial scales have peeled off and have been pushed into a fresh wound, leaving the undisinfected skin surface exposed; in these cases our tincture of iodine cannot give us the security from infection which we require."

THE SUPERSTITION AND FOLKLORE OF MENSTRUATION.

By EMIL NOVAK, A. B., M. D.

From the very earliest times the phenomenon of menstruation has been the subject of much speculation and study. In view of the many advances which have been made in our knowledge of other gynecological problems, therefore, it is rather surprising to note how little of a definite nature has been learned as to the cause and significance of this manifestation.

The history of our knowledge of this subject reflects in an interesting way the changes which have been gradually brought about in our methods of studying such problems. The earliest ideas as to the nature of the menstrual process represent a curious blending of speculation and superstition, with very little foundation of real fact. The element of mystery in the phenomenon seems to have inhibited intelligent efforts to study it. Apparently, there was a general acceptance of the depressing dictum later enunciated by Colombat "The mystery of menstruation will be forever covered with a veil that cannot be completely removed." On the other hand, it is gratifying to note that the scientific methods of our own generation have already yielded splendid additions to our knowledge of this problem. Much has thus been done to dispel the numberless superstitions which formerly befogged the subject in the minds of both the laity and the profession.

Many of these old beliefs concerning menstruation are of interest, and I have thought that it might be well worth while to gather some of them together and present them in this brief paper.

Even before the time of Hippocrates, menstruation seems to have been looked upon as a cleansing process—a periodic purging of the blood from filth and impurity. The very name given by the Greeks to the process of menstruation (*κάθαρσις*, *catharsis*) is indicative of this belief in the cleansing function of the menstrual flow. It is still the popular conception among the laity, and, perhaps, among a certain proportion of the profession. The disagreeable odor of menstrual blood may be in part responsible for this belief.

Pliny speaks of the menstrual blood as being "a fatal poison, corrupting and decomposing urine, depriving seeds of their fecundity, destroying insects, blasting garden flowers and grasses, causing fruits to fall from branches, dulling razors, etc." (Lib. VII Cap. 15.) He also states that the dog that licks menstrual blood becomes mad, although, curiously enough, as we shall see, menstrual blood was later recommended as a cure for the bite of a mad dog. He says, further: "If a woman strips herself while she is menstruating and walks round a field of wheat, the caterpillars, worms, beetles and other vermin will fall off from the ears of corn." Metrodorus,

of Scepso, tells us that the discovery was first made in Capadocia, and that, in consequence of such multitudes of cantharides being found to breed there, it was the practice for women to walk through the middle of the fields with their garments tucked above their thighs; that in other places, again, it was the usage for women to go barefoot, with the hair dishevelled and the girdle loose. Due precautions must be taken, however, that this is not done at sunrise, for, if so, the crop will wither and dry up." Astruc is another author who speaks of the ancient belief that the menstrual discharges were so venomous that "they withered and dried up the flowers, marred liquors, tarnished looking-glasses, with several other astonishing effects."

According to Pliny, bees are said to have an especial aversion to a thief and to a menstruating woman, a glance of such a woman's eyes being sufficient to kill a swarm of bees. Horses are also susceptible to this malign influence. "A mare big with foal, if touched by a woman in this state, will be sure to miscarry; nay, even more than this, at the very sight of a woman, though seen even at a distance, should she happen to be menstruating for the first time after the loss of her virginity, or for the first time while in a state of virginity. So pernicious are the properties of the menstrual discharge that women themselves, the source from which it is derived, are far from being proof against its effects. A pregnant woman, for instance, if touched with it, or if, indeed, she so much as steps over it, will be liable to miscarry."

Such beliefs are responsible for the abhorrence in which the menstruating woman was universally held. This is well exemplified in the Mosaic law: "And if a man shall lie with a woman having her sickness, and shall uncover her nakedness, he hath discovered her fountain, and she hath uncovered the fountain of her blood, and both of them shall be cut off from among their people" (Lev. XX, 18). The menstruating woman was held to be unclean for seven days, at the end of which time she sacrificed turtle-doves as a burnt offering.

Coitus at such a period was looked upon as a very grave offense. In ancient Persia the persons guilty of such an act were devoted to the fires of hell until the day of Judgment. The Zend-Avesta is full of regulations tending to isolate "unclean" women, while metrorrhagia is condemned as a crime punishable with one hundred strokes of the lash. It is said that even among modern Greeks menstruating women are denied communion in the church and are forbidden to kiss the church pictures (Ploss). The Bible makes frequent mention of menstruation, though usually in paraphrase. The word "menstruous" is employed three times, and always in the sense of unclean and repellant, as when Jeremiah says, "Jerusalem is as a menstruous woman among them."

History tells us, furthermore, that by a decree of the Council of Nice women were forbidden to enter church while menstruating, so that evidently it was not only the ignorant who entertained these peculiar notions of the uncleanness of women during menstruation. It is even said that certain surgeons would not allow menstruating nurses to assist in operations.

German peasants, according to Ploss (*Das Weib*, 1884), believe that, if a menstruating woman enter the cellar, she turns the wine of the Fatherland sour, and that if she crosses a field she spoils the growth of the vegetation. The humbler class of Jewesses are accustomed to signal their menstrual period to their husbands by a curious ritual observance. They tie bows of blue ribbons to their beds or chairs. Similarly, negroes in certain parts of Africa wear a scarf of glaring color folded three corner-wise over the bosom during the menses. Along the Congo River the "house of blood," a hut daubed with red clay, is used for the purpose of segregating the tribeswomen of each village when in this condition (Knott).

The negroes of Surinam must also, according to Ploss, live apart from their tribes during the menstrual periods. Moreover, when anyone approaches them they must call out "Mi kay! Mi kay"! "I am unclean! I am unclean." The same author also, in his monumental work, "*Das Weib*," gives innumerable other examples of this almost universal belief which exists among savage and barbarous peoples. A few other examples from Ploss may be cited of this remarkable taboo put upon the menstruating woman.

In Angola the women are obliged to wear a bandage about the head during the period of menstruation. If menstruation persists beyond this time, the woman is considered to be under the influence of evil spirits, and is punished with one hundred lashes of the whip.

Certain tribes believe that the process is dangerous, not only to others, but to the menstruating woman herself, and so they enforce a strict dietetic regime at that time.

Among the Tinnéh Indians, according to Frazer, it is dangerous for a menstruating girl to touch her head with her hand. If she finds it necessary to scratch her head, this must be done with a stick. Among some tribes she is not even allowed to feed herself, and among others she is obliged to wear, hanging from her forehead, a fringe made of shells or bones. The purpose of this is to cover her eyes, as she is especially susceptible to the influence of malicious sorcerers at this time (Crawford). Among certain races menstruating women are forbidden to eat anything that bleeds, as this would increase the severity of the flux in the transgressor. Among the Persians the women likewise are segregated at the time of menstruation. The usual period of isolation is four days, the maximum is nine days.

The Indian women of the Orinoco country in South America are obliged to fast during each menstrual period, while among the North American tribes the squaws are sequestered in separate huts during menstruation. According to Colombat, the Illinois Indians punished with death any of their squaws who failed to give notice that they were affected by the periodic discharge. In the same way Crawford mentions the case of an Australian black who killed his wife because she had lain on his blanket while she was menstruating. He himself is said to have died of terror within a fortnight.

Among some of the Hottentot tribes the women are made to paint their faces with a spectacle-like design at the time of menstruation. Many savage tribes believe that if a man by

any accident comes upon menstrual blood he will be unlucky in warfare and in all other undertakings.

Ploss quotes a work by Eckarth, published early in the 18th century, in which the virulence of the menstrual discharge is illustrated by the statement that, unlike other blood, no amount of washing can remove entirely the stain it produces upon cloths. The same author says that, if a menstruating woman looks into a mirror, the latter will forever be marked by two round defects corresponding to the eyes of the woman. This is similar to the statement of Aristotle that, if a menstruating woman looks into a mirror, not only is the polish lost, but the person who next looks into the mirror will be bewitched. Pliny, speaking of this tarnishing effect on mirrors, says that the polish can be restored by having the same woman look steadily upon the back of the mirror.

Another interesting group of superstitions has to do with the influence of the menstuous woman upon milk and the milk supply. According to Frazer, the Kaffir woman of South Africa is not allowed to drink milk during menstruation. If she does, the cows from which the milk came will die. The same custom prevails among the Bahimas. Exception is made, however, in the case of the young girl with her first menstruation. An old cow, of small value, is set aside for her use. The underlying belief in these cases is obviously that there is a sympathetic bond of some sort between the cow and the milk, and that any injury to the latter affects the cow also. A menstruating woman is even forbidden to cross the pasture, for if a drop of menstrual blood were to fall on such a place, any cow passing over it would be apt to become diseased and die.

Columella, Graaf, and Verheyen, as well as a number of the old Arabian authors, have likewise attributed those noxious qualities to the menstrual blood (Columbat). According to Moreau de la Sarthe, in his "Hist. Nat. de la Femme" (t. 2, 261), the negroes of the South Sea Islands and the aborigines of South America send their females into separate huts and keep them absolutely sequestered during the whole of the menstrual period. Some savage tribes in Africa distinguish by a red flag those huts which contain menstruating women. The color of the flag is evidently suggested by the color of the menstrual discharge.

An old author, Guarinonius, sums up these superstitions in the following rhymed rules of conduct for menstruating women:

Die Töchter lass nicht unter d'Leut, noch Hochzeit noch Tanz,
Die Verheiratheten merken besonders auf ihre Schantz,
Damit sie zu wehrender Blumens Zeit
Von ihren Männern sich schrauffen weit,
Nicht greinen, nicht zürnen, nicht schlagen umb,
Sonst schlägt das Gift in d'Glieder, und werden krumb,
Die jungen Kinder nicht viel küssen noch berühren,
In der Kuchel die Speise nicht selbst anrühren,
Nicht in die Keller noch zum Weinfass gehen,
In Gärten umb die jungen Bäumlein auch nicht stehen,
In keinen reinen Spiegel hinein sehen,
Daheyms still sitzen, dafür nehen,
Sich sonsten auch gar wol verwarren,
Das leinen Tuch hierin nicht zu fast sparen,
Damit nicht das unwissend Haussgesinde,
Das Gspor der Krankheit auf dem Boden finde.

Similar, in spirit at least, are the old lines quoted by Havelock Ellis:

Oh! menstruating woman, thou'rt a fiend,
From whom all nature should be closely screened.

Not all the older writers, it must be mentioned, participated in the view that the menstrual blood was poisonous. Aristotle believed it to be "as pure as that which flowed from any wound." Hippocrates compared it with that of a slaughtered victim ("Sanguis autem, sicut a victima, si sana fuerit mulier"). John Freind, in arguing against the prevalent theory of the noxiousness of the menstrual blood, asserts that the latter cannot be impure, "inasmuch as it is not secreted by the help of any gland, but breaks forth from the capillary arteries, and therefore retains the nature of the arterieous, *i. e.*, the most pure blood."

Although such superstitions as we have been discussing are not so common as they were formerly, they are far from being thoroughly rooted out, even in our own day. Ellis speaks, for example, of the regulations still in force in the sugar refineries of northern France, whereby women are forbidden entrance during the boiling or cooling of the sugar, since the proximity of a menstruating woman would cause the sugar to blacken. Dr. Howard A. Kelly tells me that women are not permitted to enter the silver mines in Mexico, as a menstruating woman would cause all the silver to disappear from the veins of metal. For similar reasons no woman is employed in the opium industry at Saigon, it being said that the opium would turn and become bitter if a menstruating woman were near.

To show that even the medical profession of modern times is not quite free of the influence of such superstition, Ellis quotes several letters written to the *British Medical Journal* as late as 1878. The writer of one, a member of the British Medical Association, asked whether it were true that if a woman cured hams while menstruating the hams would be spoiled. He had known this to happen twice. Another medical man wrote that, if this were so, what would happen to the patients of menstruating women physicians? Still a third wrote (*British Medical Journal*, April 27, 1878): "I thought the fact was so generally known to every housewife and cook that meat would spoil if salted at the menstrual period, that I am surprised to see so many letters on the subject in the *Journal*. If I am not mistaken, the question was mooted many years ago in the periodicals. It is undoubtedly the fact that meat will be tainted if cured by women at the catamenial period. Whatever the rationale may be, I can speak positively as to the fact."

Knott also speaks of the prevalence of a singular superstition in certain rural communities in England (Essex and Worcestershire), where menstruating women are believed to have the power of "measling" meats. Laurent, again, mentions a number of modern instances in which mysterious influences were attributed to the menstruating woman—the case of the orchestral performer on the double bass who noticed that, whenever he left a tuned double bass in his lodgings during his wife's period, a string snapped; that of the woman harpist who was obliged to give up her profession because at

her periods the strings of her harp, and always the same strings, broke; the cases in which women at this period notice the supposedly spontaneous breakage of glasses, the stopping of clocks, etc.

Many other such superstitions might be mentioned—the belief in the poisonous effect of menstrual blood upon cockroaches, the theory of Ambroise Paré, that coitus with a menstruating woman would bring forth monsters, the souring of milk by the proximity of a menstruating woman, etc.

The old belief in the dangerous qualities of menstruation, together with the disagreeable nature of the process to the woman, is perhaps chiefly responsible for the euphemistic manner in which women, especially of the lower classes, are accustomed to speak of it among themselves. As Havelock Ellis points out, the very word "menses" ("monthlies") is in itself a euphemism. Schurig remarks that in both Latin and Germanic countries, the function was commonly designated by some term equivalent to "flowers," indicating, perhaps, that it is a species of blossoming, with the possibility of bearing fruit. German peasant women, for example, according to Schurig, speak of menstruation as the "Rosenkrantz" or rose wreath. The Italian women, he further remarks, give it the more high-sounding and dignified designation of "marchese magnifico," while the Germans of higher class sometimes use the expression, "I have had a letter" to denote the advent of the period.

Similar expressions, as is well known, are made use of among many women in our own country—such expressions as "coming around," "having company," and the like. It is interesting to note that such euphemisms are employed even among savage peoples. Ellis quotes Hill Font as recording the use among the Indians of such expressions as "putting on the moccasin," "putting the knees together," and "going outside," the last evidently referring to the custom of secluding the woman in a solitary hut at this period.

There is one other of these ancient superstitions which must be commented upon, and that is the association which has always been made in folk lore between woman and the serpent. Whether it was the Satanic rôle of the serpent in the episode of the Garden of Eden which was responsible for this association with the descendants of Eve it is difficult to say, though this seems a logical assumption. In Germany it was believed up to the 18th century that if one planted in the soil a hair from the head of a menstruating woman it would be converted into a snake. Among certain tribes in South Australia menstruation is thought to be due to the scratching of the vagina by a bandicoot, which thus causes the blood to flow (Ellis). In Portugal it is believed that women during menstruation are especially apt to be bitten by lizards, and they guard against the risk by wearing drawers during the period (Ploss). It has been pointed out that in various widely separated parts of the world the snake is believed to be the original cause of menstruation, although no adequate explanation is offered for this deep-rooted superstition.

From the belief that menstrual blood is very poisonous, as was, as Ploss remarks, only a short step to the supposition

that it might exert a powerful influence against sickness. In an age when physical disease was commonly looked upon as the result of the activity of Evil Spirits, it is not surprising that the most trustworthy remedies for driving out these enemies of man were usually the most disgusting. Menstrual blood, according to Pliny, was recommended for the following diseases, among others: gout, goitre, hemorrhages, inflammations of the salivary glands, erysipelas, furuncles, puerperal fever, hydrophobia, epilepsy, worms, headache, etc. As a remedy, Velsh gave menstrual blood the name of "Zenith." It was prepared by extracting the dried blood from cloths by means of Rhein wine or vinegar.

The first napkin worn by a healthy virgin was put aside "for use in cases of plague, malignant carbuncles, and other diseases; it was damped with water and laid on the part; the discharge was also used as a topical application in acute gout" (Crawford). Avicenna recommended menstrual blood as an external application for sores of all kinds. For the cure of quartan fever Ictidas, according to Crawford, recommended coitus with a woman who was just beginning to menstruate. The same author states "that medicine men, when about to compound their medicines, were in the habit of making a saving clause that the remedy would be effective, provided no menstruating woman approached their chamber during the compounding process."

Not only as a medicament, but also as a charm, was menstrual blood considered potent. A garment, stained with the menstrual blood of a virgin, is considered in parts of Bavaria a certain safeguard against cuts and stabs. It will also extinguish fire, and is valuable as a love philtre (Ellis). Strack gives instances, occurring even in the Germany of to-day, of girls who administered drops of menstrual blood in coffee to their sweethearts, in order to retain their affections. It is even said (Ellis) that a sect of Valentinians attributed sacramental virtues to menstrual blood, and partook of it as the blood of Christ.

Pliny speaks of the general belief among the Greeks and Romans that a menstruating woman could quiet a tempest, and that she could therefore rescue a ship beset by storm and wave. Daniel Becker (quoted by Ploss) states that, if a cloth stained with menstrual blood be fixed on a pole in a field, the hares will congregate to this place in such numbers that they can easily be shot, and even caught in the hand. In certain countries, especially Italy, cloths stained with menstrual blood are said by Eckarth to have formerly been sold as charms against evil spirits. All these superstitions applied especially to the menstrual blood passed at the first period.

One more instance of the superstitious belief in the magical potency of menstrual blood may be cited from the prolific Pliny. He says: "If a man take a frog and transfix it with a reed entering its body at the sexual parts and coming out of the mouth, and then dip the reed in the menstrual discharge of his wife, she will be sure to conceive an aversion for all paramours."

A monthly purgation of impurities, through the medium of menstruation, was looked upon by many of the old writers as

necessary for the promotion of conception. As Freind pointed out, however, if this were true, "no woman would conceive except those who had undergone it, which is wholly repugnant to experience." Other authors (Astruc) suggest that conception is promoted by menstruation either by "forcibly exciting the woman to coition or by the fact that the menstrual discharge opens up the uterine canal, so that the spermatozoa have freer entrance into the uterus."

Mention must also be made of the theory of Galen and his followers, that "the menses are given to women that they may be evacuated for their health's sake and yield nourishment to the embryo when suppressed by conception." This is the view supported later by John Freind. Hippocrates himself believed that "if a woman with child have her menses, it is impossible that the foetus shall be well, because the growth of the foetus is abated by the menses." In the same belief Celsus stated that "if milk flow from the breasts of a woman with child, whatever she bears must be weakly."

Leaving aside these differences of opinion with regard to the *raison d'être* of menstruation and turning to the direct or efficient causes of the phenomenon, it is of interest to note that at least one of the theories prominently discussed among the medical profession, even up to the first quarter of the 19th century, was virtually of folk-lore origin. Certainly it was supported by no scientific observations. I refer to the theory that the rhythm of menstruation is under the influence of the moon.

The fact that the length of the menstrual cycle corresponds to one lunar month led many of the older writers to attribute to the moon a powerful causative influence on the process. "Luna vetus vetulas, juvenes nova luna repurgat." The absurdity of this theory, in accordance with which all women in the same locality would menstruate at the same time, does not seem to have appealed to them.

The celebrated Dr. Mead wrote a treatise on "the influence of the sun and moon on human beings," wherein, according to the prevailing notions of the time, he labored to show that both luminaries exert much action upon animals. In speaking of their influence on periodic hemorrhages, he says: "And this action of the moon pertains even to those quadrupeds that menstruate, for it has been observed that they generally have those evacuations about the new moon; in particular, mares

and monkeys; and so constantly that, according to the testimony of Horus Appollo, the Egyptians painted the cynocephalus to represent the moon, upon account of a certain symptom, whereby the female of this animal has evacuations of blood from the uterus at the new and full moon; and they kept monkeys in their temples in order to point out the times of the conjunctions of the sun and moon, whereon the moon's influence is apparent in all animals, provided irregularities in their way of living do not prevent it."

Among the old authors who adhered to the theory of lunar influence on the menses were Aristotle, Van Helmont, and others. Gall, while not admitting any such influence, believed that the discharge takes place generally at about the same time in all women, and that there are certain weeks in which no women are menstruating. He divides the menstrual epochs into two groups, embracing the first eight days of the first and second fortnights, respectively, *i. e.*, the first and third weeks of the month. If women happen to menstruate during the second and fourth weeks, the occurrence is, according to Gall, accidental, for after some months they again fall under the obedience of the general law.

The other theories as to the cause of menstruation which held sway during the earlier portion of the last century—the ferment theory and the well-known plethora theory of Galen—were scarcely less far-fetched than the one just discussed, but, inasmuch as they possessed at least a pseudo-scientific basis, they can scarcely be included in a discussion of the folklore of menstruation. The really scientific study of menstruation dates from the work of Négrier, in 1832. The 20th century, young though it is, has yielded perhaps the most valuable contributions that have been made to our knowledge of the cause and mechanism of this, one of the least understood of the phenomena of the human body. Modern methods of scientific investigation are gradually sweeping away the cobwebs of mystery and superstition which have accumulated about the subject in its passage down the folk-paths of the centuries. On the other hand, can we reasonably doubt that our present finely spun theories of menstruation will excite among medical historians of the future the same compassion which we now bestow upon the crude beliefs of our scientific forbears?

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

MAY 1, 1916.

1. Treatment of Neurasthenia. DR. AUSTEN RIGGS, Stockbridge, Mass.

To appear later in the BULLETIN.

2. A Demonstration of the Efficiency of Motion Pictures in Teaching Surgical Technic. DR. J. BENTLEY SQUIER, New York City.

THE LAENNEC.

MAY 5, 1916.

1. Contribution to the Study of Prognosis. DR. HERBERT M. KING, Loomis, N. Y.

To appear later in the BULLETIN.

2. The Study of Immunity to Tuberculous Infection from the Cellular or Tissue Standpoint. DR. ALLEN K. KRAUSE, Saranac Lake, N. Y.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

May 15, 1916.

1. Exhibition of Medical Portraits Presented to the Hospital. MR. BLANCHARD RANDALL.

I shall say only a few words, perhaps somewhat in the way of explanation. These pictures are to supplement the valuable Fisher collection which Dr. Kelly gave to the Hospital many years ago, and which we hope to continue with various supplements. The making of this collection was a great satisfaction. We picked up some of the pictures because they pleased us, sometimes because

they looked like somebody, or perhaps because our little group of friends at home thought it was interesting to have this or that picture. Gradually the number increased, until, through Dr. Welch's influence and the magic charm of his spirit, the thought came that these pictures would supplement the Fisher collection.

I cannot tell much about etching and engraving in a few words. I was always struck with the French word "*engraver*" which means to push a boat on the sand, and that describes exactly what etching and engraving means. To push half a dozen boats on the sand is what the engraver does with his tools on copper. In this little collection we started at about the year 1725, with some of the masters in art at that time, and traveled about two centuries, until we came to such a picture as that at the end of the line which is only about ten or fifteen years old.

In the year 1725 engraving was done on both wood and copper. Indeed, throughout the sixteenth century, the wood engraving was of a very high order. The Germans, more than any other nation, used wooden blocks. The history of engraving shows that the Chinese antedated the Germans in this art, but through the fifteenth and sixteenth centuries the Germans carried it to a high point of perfection. Later the English took up wood engraving, and still later the art fell into a mere trade to illustrate books, until in our own day, in America, Cole and Wolf have done, with wood blocks, work which has never been done before in the history of the art.

In the seventeenth and eighteenth centuries engraving had ceased to be a workman's trade and had become a real art. From the middle of the seventeenth century engraving in pure line in France, and what is called mezzotint in England, were the two mediums in which the art was brought forward. That was the highest point in the French art and perhaps the highest point in the English.

Finally, in the nineteenth century, the old etching processes that Rembrandt made so famous grew again in favor. Of recent years the use of etching and engraving, coupled with both stipple and mezzotint, has made very beautiful figures and scenes. The use of these methods in the same plate, which were very distinct in previous years, but which are now used together to get results quickly, has commercialized too much the modern work.

The French were very successful about the middle of the nineteenth century in colored engravings. These were really engravings on stone, or lithographs. In the eighteenth century the English were especially successful with portraiture.

Some of my happiest hours have been spent with these pictures and I shall hope to revisit some of these scenes again with Dr. Welch.

DISCUSSION.

DR. HURD: I hope that Mr. Randall will still feel a sense of proprietorship in these pictures and consider them as simply a loan to us. On behalf of the Hospital, I wish to thank Mr. Randall for his generous gift.

Dr. Kelly looks as though he had something to say to us.

DR. KELLY: I feel ashamed to open this unpretentious package after what Mr. Randall has given. The pictures are not only portraits which doctors might like to look at, but they are also fine examples of the collector's instinct which Mr. Randall has so well developed. These pictures are only a small portion of his magnificent collection, but they are worth feasting the eyes upon, especially the example of Larrey.

The Albinus is evidently about 100 years old and made from some old wood block. Probably a copy.

Here is a portrait of John Dalton, the founder of scientific chemistry. He belongs in this group, because all we know about color blindness we owe to John Dalton. A close look at the picture will show the earliest chemical symbols, a little black and two small white spheres, intended to represent carbon dioxide. The atomic theory dates from John Dalton

I have brought with me a few pictures to add to the collection. They have not any special artistic merit. Among others, there is Wharton, who discovered the duct which bears his name, Sömmerring, the anatomist, and this portrait of Celsius, which is, I suppose, what people imagined he looked like. Here is a portrait of Philip Pea or Parva, a little known surgeon of Paris, who lived in the latter part of 1600, and who used part of his name in his motto: *Tam solers quam parva*. Mr. Randall's portrait of Alexander Monro is better than the one I have brought. You will remember that there were three Monros. The first and second were distinguished anatomists. The last one used to come before his classes and read his grandfather's lectures on anatomy, and the members of the class were much entertained when he would read, for instance, of some event that happened when he was in Leipsic sixty or eighty years before.

I also have brought over pictures of Mascagni and Lancisi and this one of Ruysch, the great anatomist, who worked over the lymphatics and made the magnificent collection that was bought by Peter the Great, who wished to take it to St. Petersburg. On the way, however, the sailors drank all the alcohol off the anatomical specimens, and Ruysch had to go to work all over again. This is not so strange as it may seem. I well remember when I was a student in Philadelphia that Leidy's collection lost its alcohol at a remarkable rate, and Leidy had to take the alcohol and put arsenic in it in the presence of our prospector.

As I said before, I am ashamed to present these pictures in view of the splendid examples before us presented by Mr. Randall.

MR. BROEDER: I am sure that some of you know as much as, and perhaps more than, I do about what you like in pictures of great men. What we usually consider necessary for the appreciation of a portrait is that the likeness of the individual should be represented with a fair degree of accuracy. Of course, we can have no means of judging whether these pictures represent the features of these famous physicians and surgeons. The next requisite in the value of a picture is the pose—the characteristic pose which the individual assumes most of the time. That is necessary to make a good portrait. The third is the artistic treatment of the features and of the accessories, such as the hair, hands, garments, etc. That requires the artistic touch. The last requisite is technique, perfect treatment of the surfaces to represent the character of the tissues of the eyes, hair, skin, etc.

The layman's judgment of the value of a portrait, be it painted or etched, is usually affected by modern photography, and we demand in our contemporary portraits and oil paintings, and in mechanical reproductions, absolute fidelity—an absolutely faithful representation of the features—or we are not favorably impressed. These portraits cannot be judged by such standards. The connoisseur's standpoint of judging these works of art is totally different from that of the layman. It is technical and historical; he takes into consideration the difficulties the engraver had to overcome.

Of course etchings and engravings are not original productions, but are usually copies of a painting, and most of us criticize old prints because of certain shortcomings which are common to nearly all. These defects are absent in a large number of the pictures exhibited here, as this is a remarkably fine collection of old prints from the standpoint of artistic treatment and technique. Most old prints are not pleasant objects to look at for a number of reasons. We complain of a certain monotony of features; that they all look more or less alike, just as old Egyptian figures look alike; and sometimes we suspect that the artist was not very faithful in copying his man. We complain of a certain lack of expression and a fixed, lifeless appearance of the eye, and of the regions around the eye. That is a common shortcoming in most of the old prints. The conclusion we draw is that there is a certain inferiority of the artist who was commissioned to do the work. Nine-tenths of the old prints exhibited were originally painted by second-rate men, and the engravers were in the same class.

Painters like Rembrandt, Rubens, Holbein, Velasquez and Reynolds are scarce. They are usually monopolized by royalty and the princes of the church and of commerce and do not go around; so that most of the work is done by second-grade men. I have even been impressed with the fact that first-class artists did not copy the human face with a remarkable amount of accuracy. For instance, in studying the portraits that Rembrandt painted of himself, we are struck with the fact that they do not look alike, and so conclude that Rembrandt took liberties when painting portraits. A great many painters prefer a good picture to a portrait. They prefer to make harmony in tints and a perfect composition in lines rather than a faithful representation of the features of the man they are painting.

As I said before, what we admire most in modern paintings and modern engravings is this absolute fidelity to nature. We consider them superior as far as realism is concerned; and that is right. The reason for this superiority of modern work is of course the camera. Photography has given to the artist a means of judging the exactness of his work and has had a beneficial effect upon the accuracy of his work. I do not mean to argue that photography is by any means equal to painting, but there is no question but that accuracy in regard to form is provided by the work of the camera. An artist would be ashamed to let a picture go out that does not look like the subject, when the photograph shows him what it should be.

All the pictures shown here, with the exception of one or two, are done without photographic aid. All true art must be done without photographic aid. To see nature through the artist's eye is a joy to man. There is no question but that a May morning described by a poet is a very different thing from a May morning seen by a farmhand; and an intellectual face represented by a Sargent or a Joshua Reynolds is a more pleasing object to look at than a face as seen by a floorwalker, let us say. The highest type of portraiture, therefore, is a perfect balance between the subjective view of nature, which is the artist's view of it, where you have evidence of the artistic feeling in every square inch of the canvas, and at the same time absolute fidelity to nature, so that the impression will be satisfactory.

These etchings, engravings, mezzotints and lithographs were done, as I have said, without the aid of the camera. All of these were first painted, drawn or sketched, and in the reproduction each must have suffered a little in veracity, as each worker takes a little liberty, although perhaps unconsciously. Each painter has undoubtedly taken liberties with the form, for each painter likes certain features. If one painter is struck by an extraordinarily pleasing eye, he dwells on that and paints the feature as he sees it. This experience is found in every work of art. The artist puts his soul into the painting and shows the object as he thinks it ought to look. This toying with the truth does not affect the same features in every case. The engraver may be struck with the charm of the contour of the nose, so he takes liberties with the nose, and gets a gradual departure from the truth, with the result that the final engraving may not in the least resemble the person it was intended to represent.

These are the difficulties of the first class, but there are also other difficulties. For instance, almost all of the originals were life size, and the engraver had to reduce that life size portrait to perhaps one-half, one-third, one-quarter or even one-fifth the measurements of the human face. That is a very difficult process, as very slight deviations in the proportions of the human face absolutely ruin the likeness of the face. The engravers have to work without the aid of the camera, and not only that, the entire process is reversed. What is right in the portrait is left in the plate, and the engraver must work in a mirror, reversing every line. That is not a method which makes for accuracy. The most important parts of the portrait are the nose, eyes and mouth, and it is interesting that it is not so much the individual feature—that

is, the eye itself or the nose—as the juxtaposition of the two which makes for likeness. The least difficult thing is technique. As I said, the engraver never knows exactly what he is doing, because he does not see the picture while he is engraving as it is to appear in the print. It is reversed, and he has a black ground on which the drawing appears as bright, coppery-red lines. This is often a disturbing factor. He is compelled to take frequent impressions to see what the final results will be. This difficulty is not shared by the lithographer, who works on a stone of a greyish color on which he draws with a black, oily crayon or oily ink. Some of the portraits here are lithographs and are remarkably well done. Lithography is of course a more recent method, whereas engraving on copper is centuries old. The mezzotint portrait before us shows evidence of photographic aid. By the expression of the face, it can be seen that the engraver controlled his work with the aid of the camera.

DR. WILLIAM H. WELCH: We are all deeply indebted to Mr. Randall for this delightful gift to supplement the Fisher collection, which we owe to the generosity of Dr. Kelly. It is good to be surrounded by portraits of medical men and to cultivate an interest in the iconography of medicine. We have endeavored here to create that sort of an atmosphere. It is not always perhaps best secured by efforts which seem to be most direct for the purpose, but sometimes by indirect methods of attack you may inspire in the student an interest which adds much to the life and enjoyment of the physician in his profession, and which makes all the difference between the practice of medicine as a profession and as a money making trade.

Medical portraiture is a specialized subject and I cannot claim any expert knowledge of it. One of the most famous medical paintings in the world is Rembrandt's "School of Anatomy." Dr. Garrison has selected another "School of Anatomy" to illustrate his excellent book on the history of medicine, and there are several others. The Guild pictures of the seventeenth century are also extremely interesting. The greatest of those are the Franz Hals pictures in Holland. I recall visiting a hospital in Delft where there was a magnificent Guild picture of medical men.

Mr. Broedel has presented very delightfully the artistic side of portraiture. Those interested in history and biography find an interest in portraits in general quite apart from the artistic merits of the picture. I know of no one who has expressed that quite so well as Carlyle in one of his letters written in 1854. I do not know that I have ever seen a better expression of the kind of interest attached to a portrait.

I am somewhat at a loss as to what to say on this occasion. A number of thoughts have occurred to me, and one is: Whose likeness is apt to be perpetuated by a painter and especially by one of the great masters of painting? What doctors are likely to be painted by Holbein, or Van Dyke, or Sir Peter Lely, Sir Joshua Reynolds or Gainsborough? What sort of a record would we find if the names were selected on the basis of the preservation of the likeness of such great physicians? One can determine that by looking over the names of the great surgeons and physicians to see if they were ever painted and, if painted, whether by first class or cheaper artists. Certain ideas occur to one. Many probably took no interest in being painted. Others may have been connected with a hospital or an institution, or perhaps made some benefaction, and may have been painted at the solicitation of the authorities of that institution. We find here, for instance, a wonderful portrait of John Ash painted by Sir Joshua Reynolds. John Ash was very active in founding a hospital, which is seen in the background of the picture. He afterwards went to London to live, and the trustees of the hospital thought it would be wise to perpetuate the portrait of John Ash, who was not a figure of any importance in the history of medicine, but who founded a hospital and so got his portrait painted. There is another excellent portrait here of

a man I never heard of before—Remmett, a Plymouth physician. He was very active in founding a medical society in Plymouth, and so he lives for all time in this fine picture. Then again, a man may have done some great service, like Woodville who went to France with the first vaccination treatment. The people in France subscribed for this interesting portrait of Woodville, and he deserved it.

Again, I think you will suspect that the great, wealthy and fashionable practitioners are pretty sure to have been painted, and that indeed is the case. There is no portrait of William Heberden that compares with the portrait of Richard Warren his contemporary, who was a fashionable physician in London, but who contributed nothing to medicine; whereas Heberden's is one of the great names in medicine. Warren had a large practice and was a good doctor in that day. He made more money than anyone else prior to his time, and he was painted by Gainsborough and also by others.

The great surgeons of the early part of the nineteenth century were deserving of being perpetuated. Sir Astley Cooper and Abernethy were sure to have been painted by the leading men of their time.

From that point of view, it is somewhat interesting just to run over the list. I have made a memorandum, not very accurate, of English physicians, beginning with the early part of the sixteenth century, Linacre, Kaye, or Caius, and Sir Theodore Mayerne. Then in the early part of the seventeenth century there were Harvey, Burton, Glisson and Mayo, who typified the spirit of their day. In the eighteenth century, the days of Steele, Addison, Pope, Pryor and Gay, the doctors who belonged to the same circle, and who held their own there, were Garth, Arbuthnot, Meade and of course John Radcliffe. This takes us up to the days of Matthew Baillie and Sir Henry Hallford. Matthew Baillie was painted beautifully, but Hallford was the figure of the day in medicine.

It is interesting to think of who were the great painters at the same periods. What a glory to have been painted by Holbein, or later by Van Dyke, or Sir Peter Lely or Sir Godfrey Kneller. Then comes the English school of the eighteenth century with such great names as Sir Joshua Reynolds, Gainsborough and Romney, with Raeburn in Scotland. Remembering these names, it is worth considering how the great doctors fared. Who was painted by Holbein? Sir William Butts! It is a wonderful picture, indeed, one of the greatest in the world. He was painted twice by Holbein, and his wife was also painted. Butts was the Court physician to Henry VIII and had great influence with him, but he contributed nothing to the advancement of medicine. However, he is in one of the most famous pictures in the world, that of Henry VIII giving the charter and seal to the Barber-Surgeons' Corporation. This was founded in 1540 and the picture represents John Chambre, with Butts on his right hand. The King is handing the charter to Thomas Vicary. Dr. John Chambre is perhaps the only one you have heard a little about. Butts was not the founder of the corporation, but Chambre was, and Linacre was one of its great names. There is a separate picture of Chambre by Holbein, which hangs in the galleries in Vienna. Linacre was also painted and the portrait is attributed to Quentin Matsys, but this is not probable. There are several portraits of Caius, or Kaye, but none by artists who were very well known.

Sir Theodore Mayerne was undoubtedly the leading practitioner of his day and a most interesting man. He comes off pretty well. There is a beautiful drawing in color of him by Rubens in the British Museum. Harvey was painted by Cornelius Johanssen, and there is an oil painting of Harvey, which is probably contemporary, in the Hunterian Museum in Glasgow.

There is a very interesting painting of Sir Charles Scarborough, the physician of Charles II, painted for the Barber-Surgeons' Company, by Robert Greene. Then comes Sir Francis Prujean, who

lived in the middle of that century, who was president of the Royal College of Physicians, and who was painted by a quite insignificant painter named Robert Streeter. Pepys says of Streeter: "A very civil little man and lame, but he lives very handsomely." Streeter was eulogized in a poem, from which I have taken two lines:

"That future ages must confess they owe
To Streeter more than Michael Angelo."

There is a portrait of Glisson, but the painter is not known. Boyle was a very busy man, who did not care very much about being painted, although there is a portrait of him by Frederick Kerseboom.

Who was painted by Van Dyke? Sir Kenelm Digby, who figures in the practice of medicine by his quackery. Valentine Greatrakes was another great quack of that period. There is a very interesting portrait of him by William Faithorne. The seventeenth century was, if anything, characterized by more quackery than the period in which we live. I think you can establish the thesis that charlatany flourishes rather in ratio to the development of science. All periods of great scientific enlightenment are always characterized by great charlatany and quackery. This was true of the eighteenth century and it is true to-day. Greatrakes was a wonderful quack.

The best of the Scottish group were of course painted by Raeburn. Sir Hans Sloane was repeatedly painted by Kneller. Radcliffe was also painted by Kneller, as was also Sir Samuel Garth, a member of the Kit-Kat Club, whom you will remember from the interesting paper presented here by Dr. Harvey Cushing some years ago. There is also a drawing of Garth by Hogarth, which is of course very interesting.

Richard Wiseman was the first really great English surgeon. He was very much admired by Dr. Johnson. There is a very fine miniature of him by Samuel Cooper. Cheselden was painted by Richardson. William Hunter was admirably painted by Sir Joshua. Percival Pott was also painted by Reynolds, and there is an excellent portrait of him by Romney. Sir Cæsar Hawkins, who was not a great man, was painted by William Hogarth.

The man who took the place of Kneller during the same period in Scotland was Medina, a Spaniard, who painted Archibald Pitcairn. Alexander Monro *Secundus* was painted by Raeburn, who is sometimes called the Scottish Reynolds. He was a most interesting painter and a man whose fame has steadily increased.

Among the portraits exhibited to-night, one of the earliest is that of de La Mettrie, a physician celebrated in the history of philosophy. He advanced the most extreme mechanistic view of man that I suppose has ever been taken. His great work is called *La bonne machine*, and he looked upon man as being nothing more than a piece of machinery. He could not live comfortably in France, so he went to Holland, which was quite a refuge at that time; but he did not remain there very long and traveled still farther to find a congenial resting place.

Claude Perrault is a very interesting figure in the seventeenth century. He was a physician who practised and wrote, and he was also a great architect. It is very interesting to collect the performances of physicians outside of their profession. In that respect we can almost claim Sir Christopher Wren, who belonged to the group of doctors at Oxford in 1650, the group which led to the formation of the Royal Society. It was a most fascinating period, and Sir Christopher Wren, whose name simply occurs to me, was one of the greatest of architects. So also with Claude Perrault. He was a brother of that Charles Perrault, whose fairy stories are models of their kind.

Here is a portrait of Huyghens, who was a great mathematician, anatomist and physicist. He made wonderful studies in physical optics and prepared the way for Newton's corpuscular theory and for Sir Thomas Young, the great physician who brought forward the wave theory of light.

Philippe Colot was one of the great lithotomists of that period. Those were the days when cutting for stone was a separate specialty. There were many traveling quacks, and some very interesting characters among them.

Albinus was one of the greatest anatomists, teachers and illustrators who ever lived. He was a professor in Leyden, a younger contemporary of Boerhaave. It was to Leyden in this period that the Scotch and English students went.

Sir Thomas Millington was a professor at Oxford and president of the Royal College of Physicians. He belonged to that group I have spoken of, "the invisible college," and was one of its most distinguished members. Indeed, I think anyone Sydenham thought was a good doctor must have been, as he did not care much for most of his colleagues.

Here we see Thomas Pellett, a physician in the first half of the eighteenth century. He was the friend of Radcliffe, Arbuthnot, Freind and Sir Hans Sloane. Arbuthnot is perhaps the best known of the group on account of his intimacy with Pope.

Alexander Monro the Second was the great Monro. From 1725 until we approach 1840, the three Monros were professors of anatomy at the University of Edinburgh. The first one was a very eccentric man. The second was very distinguished; he was trained in Germany and was a most admirable character. The third was not to be classed with either of them. They resisted efforts at reform in medical education in Scotland, and especially resisted the establishment of a chair of surgery, which did not exist until well on in the nineteenth century.

Here, by Sir William Beachy, a contemporary of Sir Thomas Lawrence, is a portrait of Sir Everard Home. The indelible stain rests upon his name of having destroyed the valuable manuscripts of John Hunter.

And here is a most interesting portrait of William Woodville, of whom I have already spoken. He plays a great part in the introduction of vaccination. Indeed, the anti-vaccinationists contend that, if it had not been for Woodville, vaccination would never have succeeded. He was also an eminent medical botanist and wrote a botany in four volumes. He was physician in the inoculation hospital in London. At first he was opposed to Jenner, but afterwards became one of the best workers. He obtained cow-pox lymph and at this hospital practised vaccination.

Henry Harrington's portrait is very interesting. It was painted by Thomas Beach, who was a very actively employed painter of his day. Harrington was a physician in Bath and is best known for his history of music. He comes straight down from Sir John Harrington, of whom I am sure some of you know.

Joseph Black's is perhaps the greatest name on the list. He was both a chemist and a physicist. Never did a medical student publish a graduating thesis comparable to his. He was a medical man and a pupil of Cullen. He was a professor of chemistry first in Glasgow and later succeeded Cullen in Edinburgh. He was the discoverer of what was, perhaps unfortunately, called latent heat. He was an excellent teacher and an active man in the wonderful circle in Edinburgh.

I shall pass over Vogel, who was a professor of anatomy and medicine, and John Heaviside, who was surgeon extraordinary to the King and who collected a museum. This was in the period after John and William Hunter, when all were collecting anatomical specimens.

Here is a lovely picture of Matthew Baillie, the nephew of John and William Hunter and the brother of Joanna Baillie. He was taught by William Hunter and succeeded him in the Great Windmill Street School. From teaching and investigating work, he became the leading physician of London. His *Morbid Anatomy* published in 1795, while it has not the significance of Morgagni's, is the first work devoted exclusively to that subject and presented it just as we do to-day.

We next come to Lucas, who gets several pages in the Dictionary of National Biography. He was a painter as well as a doctor.

Berthollet was a great chemist, indeed he was one of the founders of physiological chemistry. He was painted by Rembrandt Peale, a son of Charles Wilson Peale. There were about eight of the Peales who were painters. Charles Wilson called his sons by such names as Rembrandt, Raphael and Titian, and they all painted. Rembrandt studied with Benjamin West and afterwards worked in Paris. He was an extraordinarily versatile man.

A most fascinating doctor was John Mudge. He was a Plymouth man and one of the famous village physicians of England. Mudge well deserves to be perpetuated. He was quite interesting, as was his father before him, Zacharias Mudge, the subject of that wonderful Johnsonian epitaph. The son was the friend of Joshua Reynolds and Samuel Johnson, who visited Plymouth and were entertained by Mudge. Johnson used to consult Mudge about his ailments. At one time an operation was proposed and he wrote to Mudge something in this line: "It probably is painful, but is it dangerous? I hope to bear the pain with decency, but I am loath to subject myself to much danger." Mudge was a charming man, and the London physicians used to send their patients down to him on account of the life-giving qualities of his talk and personality. He was painted by Sir Joshua Reynolds.

Joshua Brooks was head of one of the private schools. This movement began in the eighteenth century and led to the Great Windmill Street school. There were many other schools and one of the most celebrated was Joshua Brooks'. Most of the Americans studied in these schools, and when the time came to do away with them and have hospital schools, there were all sorts of complications.

Larrey is celebrated as an oculist. Jenner, Dalton, Remmett, Cuvier and Cooper are also interesting. Cooper was a professor of surgery at the University College and wrote a surgical dictionary. Owen was a prosecutor for Abernethy.

Here is a beautiful portrait of Abernethy, who was one of the greatest teachers who ever lived. It is interesting to contrast Abernethy with his contemporary Sir Astley Cooper. They were very different men. Abernethy is to be regarded as the custodian of John Hunter's ideas and thoughts. He expounded Hunter's doctrines and especially that doctrine of the constitutional origin of local diseases, the treatment for which was characteristic of English medicine for a long time—dieting the patients and giving mercury, calomel and purges. All that comes from Abernethy, who was one of the great characters of medicine and who made a tremendous impression on his pupils.

Sir George Johnson's is another example of a painting having been done at the instance of a hospital and the pupils. His beautiful picture was painted for King's Hospital, which he served for many years. Johnson's name is identified with Bright's disease which he studied for a long time.

I have not begun to express really the interest there is in tracing the history of medicine as one can from these portraits here. I hope I have indicated to you how fascinating it is to take any one of these men and fit him into his environment, and how much it adds to that kind of study to have these charming portraits with us.

DR. ARNOLD C. KLEBS: "Art is long, but time is short," to paraphrase Hippocrates, and so I shall not occupy more of your time than to express my warm appreciation for having been allowed to be present on this unique occasion. Mr. Randall's words of presentation seemed to carry a message of particular significance. In these strenuous times a collector so rarely seems to have time to love his collection. And somehow, as he reviewed one after the other these beautiful prints, I could picture him sitting over them day and night, viewing with the eye of the *connoisseur* these delightful products of the artist's point and

burnisher, and treasuring their possession. May they find this same affectionate interest and care in your keeping!

Inspiring also were the words of Mr. Broedel, artist himself and master in the technique of medical illustration. Your interesting "Institute of Art in Medicine," which he heads, daily draws together artist and physician in useful cooperation. And those of Dr. Welch, whose admirable talk has animated these gentlemen on the wall, so that they have come down among us from their frames, closer to our scrutiny and simple human understanding.

It all brings to one's consciousness the very close relationship that really exists in the aims of artist and physician. We should not fail to remember it. Our common aim, primarily, is toward Truth and its expression. For what end? For our own satisfaction, for our sustenance, and to bring artistic joy or health, in our case, into the lives of others. In the last analysis it leads to same results, except that the artist has what we lack too much—the inspiration of beauty. In the Middle Ages, in Florence and other cities, one of the major guilds united both physicians and painters. At first they also were drug sellers and color grinders. Then in that general aim to make medicine an exact science, the physician has more and more drawn away from the artist. When Dr. Streeter, not long ago, told us here of the close cooperation of Florentine artists and physicians, it occurred to me how much true art often loses by a one-sided concentration on technique, we physicians on instrumental precision, the artist on new pigments, binders, etc. It seemed to me time for a new guild of physicians and artists. Something must bring back into our busy lives the inspiration of beauty, bring us to the warm delight in line, form and color, make us dissatisfied with that "beauty" which Sunday newspapers and artistic posters inflict upon us daily.

To illustrate the rôle of artists in the divulgation of medical thought and the various means employed in historical sequence, I have arranged at the Surgeon-General's Library a little exhibition, selecting from that fine collection the most characteristic specimens in black and white, as well as in colors. It may perhaps interest some of you to examine these examples, some of which are exceedingly rare.

Medical Portraits in Etching, Engraving and Mezzotint Given to The Johns Hopkins Hospital by Mr. Blanchard Randall.

- Abernethy, John, 1764-1831. (Abernethy on portrait.) After Lawrence, by Bromley.
- Albinus, Bernardus Siegfried, 1696-1770. Car. de Moor pinx. I. Iac. Haid sc. et excud. (or J. J. Haid.)
- Ash, Joannes, 1723-1798. Painted by Sir Joshua Reynolds. Engraved by Bartolozzi.
- Baillie, Matthew, 1760-1823. Painted by J. Jappner. Engraved by Charles Turner.
- Béclard, Pierre Augustin, 1785-1825. Lith. de Delpech à Paris. Z. Belliard.
- Berthollet, Claude Louis, 1748-1822. Rembrandt Peale pinx. Allais Scot.
- Black, Joseph, 1728-1799. Engraved by Jas. Heath from a picture by Raeburn.
- Bourgeois, Louise, dite Boursier, 1563-1636. Engraving.
- Brookes, Joshua, 1761-1833. Painted by T. Phillips. Engraved and published by James Fittler.
- Burnie, Alexander, about 1825.
- Collet, Philippe (see Colot, Philippe). Edelinck, sc.
- Cooper, Samuel, 1780-1848. Painted by Andrew Morton. Engraved by Henry Cousins.

- Corvisart, Jean Nicholas, 1755-1821. Gr. Lith. de Delpech. Bazenjne.
- Cuvier, Georges Léopold Chrétien Frédéric Dagobert, le baron, 1769-1832. Painted by W. H. Pickersgill in 1831. Engraved by Geo. Doo, 1840.
- Dalton, John, 1766-1844. Allen pinx. Worthington sc.
- Des Genettes, René Nicolas Dufriche, 1762-1837. Lith. Maurir. S. Lith. de Delpech.
- Dubois, Antoine, baron, 1756-1837. Boilly pinx. Gautier sc.
- Faraday, Michael, 1791-1867. Painted by H. W. Pickersgill. Engraved by S. Cousin.
- Forlenze, J. M. A. Vallin, pinx. Gautier, sc.
- von Graefe, Friederich Wilhelm Ernst Albrecht, 1828-1870. Lith. von C. Wildt.
- Guersant, Médecin. Lith. de Ch. Motte.
- Harrington, Henry, 1729-1816. Painted by Thomas Beach, 1799. Engraved by Charles Turner.
- Heavside, John. J. Zoffany pinx. Rich. Earlom sc.
- Home, Sir Everard, Bart., 1763-1832. Painted by Sir W. Beechey.
- Howard, John, 1726-1790. Engraved by Edmund Scott from an original picture by Mather Brown.
- Hughens. Drevet excud. Edelinck eques sc.
- Huxley, Thomas Henry, 1825-1895. Painted by John Collier, 1883. Engraved by Eliot Farnoy (?).
- Jay, Antoine, 1770-1854 (?). (A. Jay on portrait.) Gosse pinx. Z. Belliard.
- Jenner, Edward, 1749-1832. Wm. Hobday pinx. Wm. Skelton, sc.
- Johnson, Sir George, 1818-1896. Painted by Frank Holl. Engraved by Frank Short.
- Larrey, Dominique Jean, le baron, 1766-1842. Lith. de Delpech.
- Lucas, Charles, 1713-1771. L. Reynolds pinx. I. McArdell fecit.
- de La Mettrie, Julien Offray, 1709-1751. G. F. Schmidt ad vivum pingebat et sculpebat.
- Millington, Sir Thomas, 1628-1704. London, pub. by Dr. Thornton, 1807.
- Monro, Alexander, 1733-1817. Engraved by Jas. Heath from a picture by Raeburn.
- Mott, Valentine, 1785-1865. Lith. by F. D'Avignon, 1856.
- Mudge, John, 1720-1793. Painted by Sir Joshua Reynolds. Engraved by W. Dickinson.
- Owen, Richard, 1804-1892. Painted by H. W. Pickersgill. Engraved by Wm. Walker.
- Pellett, Thomas, 1671-1744. N. Dath pinx. I. Faber fecit.
- Perrault, Claude, 1613-1688. Vercelin pinx. G. Edelinck, sc.
- Physick, Philip Syng, 1768-1837. Engraved by J. B. Longacre from a sketch by Mr. T. Sully.
- Remmett, Robertus Butler. From an original portrait by John Ball. Engraved by S. W. Reynolds, 1823.
- à Roy, Cornelius Henricus, 1750-1833. G. Ritter, del. L. Portman sc. J. Allart excud.
- Vogel, Benedict Christian, 1745-1825. Hessel del. F. Elias Haid fecit.
- Woodville, William, 1752-1805. (W. Woodville on portrait.) Ansiau del. Perrot sc.
- Wharton, Thomas, 1610-1673. From a rare print.

Medical Portraits Given to The Johns Hopkins Hospital by Dr. Howard Atwood Kelly.

- Brunyer, D. Abel, 1573-1665. Petrus Landry, sculp., 1661.
- Butler, William, 1535-1617. Harding, del. Clamp sc. Publ. Oct., 1796, by E. & S. Harding, Pall Mall.
- Celsus, Aurelius Cornelius. (Celsius, A., on portrait.) Jefto von Böttger aus Dresd.
- Garth, Sir Samuel, 1661-1719.

- Haller, D. Albertus, 1708-1777. (von Haller, Albrecht.) (P. G. Werlioh.)
- Lancisi, Joannes Marias, 1652-1720. (Lancisi, Giovanni Maria, 1655-1720, Garrison.) Sebastian Conca, pinx. lac. Frey sc., Romae, 1718.
- Mascagni, Paolo, 1752-1815. Stefano Ricci, sculpi. Roberto Focosi disegno. Giusseppe Buccinello incise.

- Monro, Alexander, 1732-1817 (Monro, Alexander Jun., secundus, 1733-1817). Engraved by Jas. Heath from a picture by Raeburn.
- Peu, Philippe, -1707. (On picture, Peu, Philip.) S. Thomas-sin ad vivum delineabat & sculpebat, 1693.
- Ruysch, Fredericus, 1638-1731. I. Wandelaar ad vivum delin.
- Sömmerring, Samuel Thomas, 1755-1830.

BOOKS RECEIVED.

- The Jews in the Eastern War Zone.* 1916. 12°. 120 pages. The American Jewish Committee, New York.
- Autoplastic Bone Surgery.* By Charles Davison, M. D., and Franklin D. Smith, M. D. With 174 illustrations. 1916. 8°. 369 pages. Lea & Febiger, Philadelphia and New York.
- Handbook of Massage for Beginners.* By L. L. Despard. Oxford Medical Publications. 1915. 12°. 247 pages. Henry Frowde, London; Hodder & Stoughton, London.
- The Pathology and Treatment of the So-Called Nervous Asthma.* By J. B. Berkart, M. D. 1916. 8°. 54 pages. Humphrey Milford, Oxford University Press, London, Edinburgh, Glasgow, New York, Toronto, Melbourne, Bombay.
- Treatise on Fractures.* By John B. Roberts, A. M., M. D., F. A. C. S. and James A. Kelly, A. M., M. D. With 909 illustrations: radiograms, drawings and photographs. 1916. 8°. 677 pages. J. B. Lippincott Company, Philadelphia & London.
- Nerves.* By David Fraser Harris, M. D., C. M., B. Sc. (Lond.), D. Sc. (Birm.), F. R. S. E. Home University Library of Modern Knowledge. 1913. 16°. 256 pages. Williams and Norgate, London.
- Transactions of the American Surgical Association.* Volume the thirty-third. Edited by John F. Binnie, M. D., Recorder of the Association. 1915. 8°. 825 pages. Printed for the Association, Philadelphia.
- The Principles and Practice of Perimetry.* By Luther C. Peter, A. M., M. D., F. A. C. S. Illustrated with 119 engravings. 1916. 8°. 232 pages. Lea & Febiger, Philadelphia and New York.
- Diagnostic Methods Chemical, Bacteriological and Microscopical.* By Ralph W. Webster, M. D., Ph. D. Fifth edition, revised and enlarged with 37 colored plates and 171 other illustrations. [1916.] 8°. 758 pages. P. Blakiston's Son & Co., Philadelphia.
- International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by H. R. M. Landis, M. D. Twenty-sixth series. Volume I, 1916. 8°. 326 pages. J. B. Lippincott Company, Philadelphia and London.
- Manual of Vital Function Testing Methods and Their Interpretation.* By Wilfred M. Barton, M. D. 1916. 12°. 255 pages. Richard G. Badger, Boston; The Copp Clark Co., Limited, Toronto.
- Nervous Children, Prevention and Management.* By Beverley R. Tucker, M. D. 1916. 12°. 147 pages. Richard G. Badger, Boston; The Copp Clark Co., Limited, Toronto.
- Michigan State Board of Health.* Forty-second Annual Report of the Secretary of the State Board of Health of the State of Michigan for the fiscal year ending June 30, 1914. 1915. 8°. 159 pages. Lansing, Michigan.

- A Laboratory Course in Serum Study; Bacteriology 208.* Being a Series of Experiments and Diagnostic Tests in Immunology Carried out in an Optional Course Given to Medical and Graduate Students in the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York, by the Writers. Hans Zinsser, M. D., J. G. Hopkins, M. D., Reuben Ottenberg, M. D. 1916. 8°. 184 pages. Macmillan Company, New York.
- The Basis of Symptoms. The Principles of Clinical Pathology.* By Rudolph Krehl. Authorized translation from the seventh German edition by Arthur Frederic Belfield, Ph. B., M. D. With an introduction by A. W. Hewlett, M. D. Third American edition. 1916. 8°. 517 pages. J. B. Lippincott Company, Philadelphia and London.
- The Institutional Care of the Insane in the United States and Canada.* By Henry M. Hurd, William F. Drewry, Richard Dewey, Charles W. Pilgrim, G. Alder Blumer, and T. J. W. Burgess. Edited by Henry M. Hurd, M. D., LL. D. Volume I. Illustrated. 1916. 8°. 497 pages. Johns Hopkins Press, Baltimore, Md.
- Pulmonary Tuberculosis.* By Maurice Fishberg, M. D. Illustrated with 91 engravings and 18 plates. 1916. 8°. 639 pages. Lea & Febiger, Philadelphia and New York.
- Clinical Laboratory Technic for Nurses.* By Anna L. Gibson, R. N. 1916. 12°. 194 pages. Whitcomb & Barrows, Boston.
- Man—An Adaptive Mechanism.* By George W. Crile, F. A. C. S. Edited by Annette Austin, A. B. 1916. 8°. 387 pages. The Macmillan Company, New York.
- New York University Laboratory of Surgical Research. Studies in Surgical Physiology from the Laboratory of Surgical Research.* Volume I, 1915. 8°.
- A Report on Researches on Spruce in Ceylon 1912-1914.* By P. H. Bahr, M. A., M. D., D. T. M. and H. (Cantab.), M. R. C. P. (Lond.), M. R. C. S. 1915. 4°. 155 pages. University Press, Cambridge; G. P. Putnam's Sons, New York City.
- The Johns Hopkins Hospital Reports.* Volume XVII, 1916. 4°. 584 pages. Johns Hopkins Press, Baltimore.
- Bernhardi and Creation; a New Theory of Evolution.* By Sir James Crichton-Browne, M. D., D. Sc., LL. D., F. R. S. 1916. 12°. 72 pages. James Maclehouse and Sons, Glasgow.
- The Practitioner's Medical Dictionary.* Containing all the Words and Phrases Generally Used in Medicine and the Allied Sciences, with Their Proper Pronunciation, Derivation, and Definition. By George M. Gould, A. M., M. D. Third edition revised and enlarged by R. J. E. Scott, M. A., B. C. L., M. D. Based on recent medical literature with many tables. 1916. 8°. 962 pages. P. Blakiston's Son & Co., Philadelphia.

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TREATMENT OF NEURASTHENIA.*

By AUSTEN FOX RIGGS, M. D., Stockbridge, Mass.

No more startling diversity of opinion is to be found in any field of modern medicine than that which obtains in the realm of the so-called "functional nervous disorders." Order has been brought out of chaos in almost every other department, and treatment of symptoms has consequently been replaced by treatment of conditions, based on a sound understanding of the etiology and pathology of these conditions.

But of the functional nervous disorders the pathology is thus far purely hypothetical, for practical purposes non-existent; and the etiology still resides in the realm of vague speculation. Take, for example, that much-worn label, "neurasthenia"—under it we find the following salad of definitions:

Dana, in the 1908 edition of his book, defines it as "a chronic functional nervous disorder characterized by a morbid weakness and nervous irritability."

Burr, in Osler's System, 1910, says: "Primary neurasthenia, strictly defined, includes only a condition of pathological weakness without discoverable lesion."

Starr says, in his book of 1913: "It is a condition of exhaustion of the general nervous system, general or local"; and quotes Edinger, who believes in the cell exhaustion theory with secondary sclerotic changes.

McCarthy, in Hare's Therapeutics, 1911, says: "Essential neurasthenia may depend upon either a congenitally inefficient nervous system, or upon abuse of the nervous system."

White and Jelliffe, in their treatise, edited by Jones, in 1913, say, among other things: "It is a fatigue neurosis due to onanism." Whereas Church, in Church and Peterson's textbook of 1914, says: "It may be due to continence," and defines neurasthenia as "a nervous state marked by irritable weakness, where nervous energy, both psychomotor and organic, is reduced, so that there is less endurance and consequently more irritability."

Barker, in Forcheimer and Billings' Therapeutics, of 1915, says: "Neurasthenic and psychasthenic states are mild forms of mental disorder, and are so-called functional nervous diseases, separable from organic." He points out, however, that this is an arbitrary division. He says: "There may be material changes in the nerve cells, but too much stress should not be laid on this view." "These conditions," he further adds, "are not to be regarded as diseases *per se*, so much as nervous and mental syndromes, that is, abnormal mental attitudes and reactions."

I hesitate to swell this confusion by adding to it the hypotheses of Freud and his followers. I am quite willing to let them pass with mention, as it would not serve our present purpose.

* Read before a meeting of The Johns Hopkins Hospital Society. May 3, 1916.

to enter the unnecessarily bitter discussion which rages about their theories.

At least one has a liberal choice of hypotheses, and so can feel perfectly sure that he will have good company, whichever one he chooses.

It is no wonder, then, that there are almost as many varieties of treatment for neurasthenia as there are physicians or quacks who practice the gentle art of healing these unfortunates! I feel, therefore, very little hesitancy in setting forth, in some detail, my own brand of treatment for neurasthenia; for I know, without further reference to the literature, that at least one author from among the best will be found to lend me the comfort and support of his authority.

Eight years ago, when I began to limit my practice to treating nervous cases, finding so many contradictory hypotheses in regard to neurasthenia, or, to put it more politely, having such a very wide field to choose from, I was at a loss; so I did not choose at all, but determined to use empirical methods, and to let my hypothesis grow by experience. Thus I bent my energies toward trying to understand the personality and needs of each patient. This intensive study of the individual patients included a study of their histories from an etiological viewpoint, the effect of previous treatments, and also the effect of my own treatment, which was at first guided largely by the "cut and try" method. Upon data and impressions thus obtained, rather than upon the authority of the literature published on the subject, has my conception of neurasthenia and its relations grown, and the Stockbridge treatment been developed.

I am considering neurasthenia as covering psychasthenic and hypochondriacal sub-varieties, for I do not find any fundamental difference in these sub-varieties.

As distinguished from the psychasthenic, the neurasthenic is simply the type that is annoyed and needlessly incapacitated by his exaggerated sensations, and therefore refers his symptoms to his body.

The psychasthenic, on the other hand, though belonging to the same general category, is too acutely aware of his mental processes, is annoyed by his emotions, and therefore refers his symptoms to his mind.

The hypochondriacal variety seems to me to be an exactly similar breed of cat, and may belong to either type, but with the worry and fear element sufficiently predominating to change the clinical picture—but only superficially.

All three are the same fundamentally.

A short statement of the hypothetical conception of the nature of the disorder under discussion, as well as a brief account of the data upon which it is based, may properly precede the description of the treatment, which in turn is, I hope, the logical outcome of the former.

In studying the treatment received by my patients before coming to Stockbridge, it was soon borne in upon me that prolonged rest had regularly done them more harm than good. In fact, the more rest they had had, the more tired they seemed to have become. Indeed, many of them were all tired out resting!

On the other hand, those who had had an exercise cure were in much better condition, not only physically, but mentally as well.

Temporary results of a striking sort had, of course, often been wrought by successful treatment of this or that complicating physical condition, such as malpositions, constipation, dyspepsia, intestinal absorption, malnutrition, etc. But all these good results were striking chiefly because of their short duration and the insignificant effect they had had upon the fundamental nervous condition. A neurasthenic with a fallen stomach became the same neurasthenic with an uplifted stomach.

My patients always seemed to have derived greater and more lasting benefit from psychotherapy, regular or irregular, than from any variety of physical treatment. Ignominious to our noble profession is the fact that the orthodox forms of physical treatment, whether rest, exercise, or orthopaedic, were markedly less potent than the quack, fake physical cures, because these latter are regularly so much richer in suggestion, in the emotional stimulation of hope, and in the guarantee of faith, than are our more respectable methods.

Furthermore, the physical conditions complicating my cases proved to be of such an infinite variety that it seemed to me absurd to suppose that they could be causal. That a practically identical condition, namely, a psychoneurosis of the neurasthenic or psychasthenic type, should have resulted from a totally different physical cause in nearly every case, was not a practical hypothesis; so it died a natural, though lingering, death. In other words, whatever the physical disorders might be, it seemed clear that, both because of their unending variety and because of the negligible effect that even successful treatment of them had had upon the ever-present nervousness, they had to be considered as merely complicating or secondary occurrences.

Save for the above-mentioned mild disturbances of bodily function, a thorough physical examination of these patients discovered absolutely nothing abnormal. Clinical laboratory examinations yielded, with like exceptions, negative results as well. Even the much-maligned nervous system came through the ordeal of examination with absolutely consistent victory. Objective symptoms were always wanting. Subjective symptoms, regularly, more than made up the deficiency by being present in overwhelming numbers. Such objective symptoms as did occur always varied with each different case, whereas the subjective symptoms seemed to have a common brotherhood—a sort of family resemblance. Each succeeding case made the evidence grow stronger. Its accusing finger pointed less often to the body, until it finally rested with unflinching constancy on the mind as the guilty element.

The therapeutic mistakes of others, as well as my own errors, served only to strengthen this suspicion, and the result of changes in my own therapy finally brought about the absolute conviction that *neurasthenia is a mental disorder*, and that it should be attacked primarily as such.

Studying the statistics of my cases, I am unable to find any reliable or undeniable predisposing causes for neurasthenia.

In the family histories, insanity, alcoholism, organic physical diseases, such as rheumatism and tuberculosis, appear with just about the same relative frequency as they do in the case histories of a general medical or surgical practice. But nervousness in one or both parents occurs in 52.4%; nervousness + insanity, in 2.5%; — alcohol or drugs, in 0.3%; — constitutional diseases, in 6.9% = 76%.

A study of the occupations brings to light nothing of interest—not even a suspicious absence of occupation, much as this fact would disappoint the railers against "nervous prosperity."

As far as sex goes, in my practice the women lead the men in the proportion of three to one. However, I do not think that one can conclude from this that the condition is a difficulty exclusively or peculiarly of the gentler sex, for the average woman can leave her job temporarily with less risk of losing that job than can the average man, and this may be the reason for their predominance in my practice. Dana and Starr both state that men predominate, while other authorities call the sexes even. However, in my opinion; if it be true that women are more frequently victims, it is not because of anything intrinsic in their make-up, but because they are usually less well trained mentally than men, and therefore more apt to lose their equilibrium. (Three-fifths of my patients belong to the well-to-do class.)

As to age, neurasthenia, like other forms of functional disorder, and by this I mean disorders without gross or discoverable lesion, occurs in late adolescence and early maturity with greatest frequency. The reason for this seems to me to be that at this time of life the individual is called upon to adjust himself or herself most radically and most frequently to the changing physical and mental needs and impulses of life; is called upon to use greater skill in self-guidance, and is, therefore, more apt at these times, so to speak, to run off the tracks of normality. Of my patients, 56% were above 20 and under 50 years old, the largest number, 33%, between 30 and 40, when they applied for treatment.

I have found neither physical nor anatomical conditions peculiar to these cases. The lean possibly predominate over the fat. But then worry, the neurasthenic's special privilege, is a notorious reducer, and is an almost constant element in this disorder.

A very frequently recurring factor among the possibly predisposing causes is the personality of the patient. Something like 80% of them speak of their "temperaments" as causal. "Sensitive" or "high-strung" are the terms most commonly used by them and by their friends, and I think in the main that they are right, for temperament, *i. e.*, mental personality, is at least one clew to the situation.

So, for possibly predisposing causes my search yields only—neurasthenic parents; a time of life when changing conditions of life call for radical readjustments; and, lastly, mental personality or temperament.

Neurasthenic parents may not mean that neurasthenia is inherited. The children of these parents have lived with their parents, in the vast majority of cases, and have therefore lived under the influence of their intimate example, open to the

mental contagion of their behavior, during the most impressionable, the most suggestible, period of life, when habits of mind are formed. So it is at least a fair assumption that the parental neurasthenia has had a great, even if not the only, effect on most cases as an environmental element.

This individual peculiarity called "temperament" must, of course, be accepted as the resultant of these two forces, heredity and environment, whatever their respective relative proportion may have been in any given case. I only wish here to suggest that the frequency of neurasthenia in the family history does not necessarily mean that there is in all, or even in a majority, of such cases a hereditary taint.

Indeed, it is my belief that, like greatness, only some are born neurasthenics, whereas the greater number have it thrust upon them, by unwise training and adverse conditions of early environment, or, more rarely, bad environment in later life.

Exciting causes, according to the patients, are many, and in each case quite definite. Each case has its own pet cause. But the variety—the immense variety—to be found in the aggregate, bars any one of these conditions from the ranks of reliable causes. Often a patient will date his breakdown from an operation. It is frequently a clean appendectomy or some uncomplicated surgical procedure. But if one searches the history with care, one regularly finds that there have been a number of neurasthenic symptoms far antedating the operation—often a series of distinct breakdowns, the operation merely being the convenient opportunity for the neurasthenia to express itself frankly.

Of course, very severe illnesses and severe operations, especially when they mean weeks and months of invalidism, and also severe mental shocks, do produce cases of secondary neurasthenia. But even in such cases one wonders if the underlying neurasthenic predisposition has not, after all, played the chief causal rôle, while the severe illness or operation has played the louder and more noticeable one of opening the gates and thus bringing the formerly unrecognized condition to the surface.

Shocks, losses, unhappiness, and difficulties—either mental or physical or both—are certainly no more frequent in the histories of these people than they would be in the life stories of any group one might pick out in an ordinary community. In fact, I have often been struck by the opposite! Usually my patients have been extraordinarily well supplied with the materials of happiness, only just seasoned with the ordinary difficulties.

There are, I believe, a great many more people who go through illnesses, undergo surgical operations, meet the ordinary and extraordinary difficulties of life without developing neurasthenia, than there are neurasthenics all told.

In short, I do not believe that the fundamental cause of the disorder can be found in the quality or quantity of the environmental stimuli. Nor yet in any physical peculiarity, anatomical or physiological. It must lie in the way these patients respond not only to the extraordinary, but chiefly to the ordinary, difficulties of life.

It seems inevitable, then, that the real cause must reside in some mental peculiarity common to all these patients. I believe that in some cases this peculiarity is directly inherited, and that in most cases a perfectly normal individual acquires it very early in life by direct mental contagion from neurasthenic parents or relatives or attendants. In still others, and more rarely, it may be produced later in life by a normal individual reacting to extremely abnormal physical or mental strains. To this last type belong the cases rightly called *secondary neurasthenia*.

My conclusion, then, is that neurasthenia is primarily a mental disorder; that the disorder, in nearly all cases, is originally independent of any and all bodily conditions, and that it exists, of course, in spite of a structurally normal central nervous system.

The mental peculiarity is in part a sort of "tenderness." (William James.) It is characterized by abnormal mental sensitiveness to the quality of feelings. Pleasantness and unpleasantness, especially unpleasantness, is too important. Therefore, sensations acquire an abnormally high emotional value, and also, through malinterpretation, a false significance, and both they, and likewise the emotions themselves, become, one might say, chronically and exaggeratedly accentuated. This chronic sensory and emotional overtone leads directly to mental inefficiency, for feelings, not reason, become the rulers of action, and the expenditure of energy is turned into abnormal egocentric channels and is accomplished at a wasteful dead level of intensity. These patients always use a sledge hammer to drive a tack, or to crack an eggshell. This inefficiency, of course, results in the characteristically poor adjustment of the individual to his environment.

The neurasthenic's world becomes divided into affective categories—things and people that are unpleasant and things and people that are pleasant; things which do him good, and things which do him harm; things which require effort, things which do not. The effortful, unpleasant, possibly harmful, are contrasted with the uneffortful, pleasant, and possibly beneficial. Ambition is replaced by caution, and life becomes a fear-ridden, retreating pilgrimage, self-conscious and miserable, whose chief, if not only, object is self-preservation, not from death, but from some great bugaboo, such, for instance, as that commonest of all symptoms, "fatigue," falsely so called, and really only a heightened consciousness of bodily sensations, concentrated and colored by apprehension.

The chronically heightened emotional tone over-drives or inhibits one or many of the bodily functions, and thus the functional disturbances so familiar in these cases are established. These are usually accepted, not only by the patients, but also, I regret to say, too often by their physicians, as the fundamental causal conditions, rather than as by-products, which they really are.

Crile and Cannon have severally shown how these functional disturbances are produced in animals, by emotion acting probably through over-stimulation of the suprarenal and thyroid mechanisms.

To all intents and purposes, then, the neurasthenic is an organically normal individual. He is sound of mind and body, but this normal apparatus of his gets out of working order because it is unskillfully used and, therefore, gets out of internal adjustment, and also out of adjustment with what should be its work.

A study of the effects of various forms of treatment confirms this view. *Were neurasthenia exhaustion, rest would cure it. It does not.* Forty-nine per cent of the cases which this report covers had received definite "rest cures" before coming to Stockbridge, but still remained neurasthenic.

Were it an *inherent weakness* of the organism, not a single case could be cured. Many cases are cured.

Were it *due to physical disorders*, then physical treatment of these disorders would cure it. Physical treatment has served at best, in my experience, to change only the physical by-products. Of the cases here reported, about 50% had had dietary, orthopaedic, medicinal, calisthenic, hydrotherapeutic, or other physical measures combined with rest cures, while some 10% had had these measures without a rest cure.

Even in the secondary type of neurasthenia, when its physical cause has yielded to physical treatment, the neurasthenia is very apt to pursue its course unless directly and properly treated for itself.

The conclusion seems clear that neurasthenia is not weakness nor exhaustion; that it is neither a malady of the intestines, the heart, the stomach, nor a disorder dependent upon structural change of the nervous system; and that it, therefore, cannot be cured either by rest or by any other physical means.

The conception, then, of neurasthenia which I have drawn from experience, and which I hold as a working hypothesis, is that it is a mental disorder, probably without organic structural change, characterized by emotional overtone; by egocentricity or, more graphically, by an ingrowing attention; by mental inefficiency; by a consequently poor adjustment of the individual to his environment; and, lastly, by a great variety of disturbances of bodily functions, which item, in common with all the others, acts retroactively upon all of its fellows. Truly a typical vicious cycle!

It calls for psychotherapy primarily and for physical means only secondarily, and then only to combat the physical by-products—whatever they may be.

Psychotherapy is of many brands. I have found formal direct suggestion of very little use, save to remove such symptoms as were produced by suggestion. It seems to me to be a very inefficient and crude method and rarely, if ever, touches of itself the basis of the trouble. It is essentially a symptomatic treatment (of use chiefly in hysteria).

Informal indirect suggestion is a far more flexible instrument, but one which every intelligent physician does and should use, whatever his practice. It is, of course, only an adjunct, though an important one, to one's main psychotherapeutic efforts.

Psychoanalysis carefully, scrupulously, guarded by common sense against the personal bias, the personal symbolism and

the possible sexualism of the user, is a very useful diagnostic instrument.

We have Freud, his co-worker, Jung, and their followers, to thank for the possibilities which this method has opened to us. But his own personal symbolism, which, as it reveals itself in his work, is so repugnant to many of us in its oriental sexualism, has prejudiced us against Freud's methods. Exclude this prejudice, and with it the hypersexual symbolism, and we find much that is valuable in this method. But a so-called "thorough Freudian analysis" I have no use for. It has in several cases to my absolute knowledge done great harm—harm which in one case it took two years to remedy, though the analysis had been applied by a distinguished Freudian over a period of some two years.

At all events, I have found in psychoanalysis, when thus guarded, a valuable diagnostic tool, especially in that most important matter, the study of personality; and it frequently either blazes the way for the active therapeutics or guides it on its way.

Fundamental re-education of the patient is the weapon in which I put my greatest trust. To teach the neurasthenic what neurasthenia is, to teach him to contrast this state of mind with the normal, to show him that he can attain this normality, is, I believe, 75% of curing him. The other 25% consists in applying this knowledge to practice.

Coupled with the re-educational psychotherapy there must, of course, be rational physical treatment, based on the particular need of each patient. This part of the treatment is carried out in Stockbridge according to a definite schedule for each patient, in which exercise plays an important rôle and includes individual calisthenics, as well as out-of-door walks, golf, skating, or snow-shoeing; while rest plays a distinctly subordinate part, and is given no physiological importance whatever.

Only for complete physiological bankrupts should rest be at all an important item and, even in these cases, I have never continued it at an aggregate of over three hours daily, exclusive of the night, for more than a week or ten days. Rests, though short, should be made as perfect in quality as possible; that is, patients should be taught how to rest. In other words, they must learn how to free, not only their bodies, but also their minds from their own pernicious over-responsible and tense control.

This part of re-education is especially important for those who suffer from the syndrome called insomnia, which is no more, no less, than a fear of not sleeping, a nocturnal apprehensive restlessness, which is the cause, not the effect, of the sleeplessness.

Rests, then, are considered rather as object lessons in re-education, illustrating what non-interference and non-responsibility will do, than as important physiological items.

Occupation, both manual and intellectual, I consider one of the most important instruments of re-education, for through it one can teach efficiency more objectively and more directly than, perhaps, by any other method. For by studying a patient's way of working, one can actually see the faults in

expenditure of energy and correct them, so to speak, on the spot.

In Stockbridge we find that weaving for women and wood-carving or cabinet work for men answer the purpose admirably. Intellectual occupation, on the other hand, is varied more according to each patient's personal resources and needs. Reading, coupled with analytical summarizing, is a frequent prescription, the work being preferably on a subject closely allied to the patient's normal job.

As I have said, re-education is the method upon which we place our greatest reliance. This is carried on through a series of office visits, which are never hurried, and are therefore frequently pretty long—they average an hour, I should think. At first, until the patient is well started on his schedule, a daily visit seems best. Then one every two or three days is sufficient.

A thorough physical examination precedes treatment. I mention this, not because of the obvious fact that it is an essential preliminary to any treatment, but because I consider it the fundamental starting-point of the therapeutics of re-education, especially from the patient's point of view. A pupil must know that his teacher is himself personally familiar with the facts, otherwise he cannot be expected to have any real confidence in the teaching. This examination is also purposely and patently made the direct basis of the physical regimen prescribed, and it thus serves another obvious therapeutic purpose.

The relation of teacher and pupil being at least fairly well established, re-education proper is begun by a few explanatory talks on normal physiological psychology, without at first any reference to the patient's especial difficulties.

These talks deal with the nervous system reduced to a very simple diagrammatic form, in which it is pictured as a telephone system with the brain as central office, while consciousness is considered as made up of energies transformed and liberated by this mechanism.

As this preliminary part of the re-education is based on a definite mechanistic conception of consciousness which also expresses to a large extent, and in some detail, my own conception of the nature of neurasthenia, I am going to quote liberally from a series of pamphlets which contain in summarized form the descriptions referred to. They are written as text-books to patients, to summarize and make concrete the re-educational talks.

The first pamphlet, after describing the nervous system, and tracing a simple sensory-motor reaction, goes on as follows:

For the purpose of description, then, let us consider the field of consciousness as though it were a sheet of water, the borders of which we know by inference must exist, but which we have never seen and probably never shall see, and whose depth likewise is immeasurable. The surface of this sheet is covered by waves of various sizes, shapes and colors, and, unlike the waves of the real water of our terrestrial seas and lakes (which move in ranks and owe their size and motion to the direction and intensity of the wind), these waves are arranged in groups, the groups in families, the families in constellations, and the constellations in one great coordinated system. In this figure, each impression made upon

our consciousness from the time of birth to the present moment, is represented by a wave, and the waves are arranged in groups and systems, according to the laws of association. (This group may be made up of impressions received at a certain time, and constitutes the memory of an event; that group, of impressions having the same or similar emotional content; and the next group may be held together by some other bond of similarity.)

These groups and individual waves are in continual motion, that is, there is motion within the groups and also a general ebb and flow of the larger or smaller combinations across the whole field. Part of the movement is due to the continual formation of new combinations from the old. This group or that may dissolve and its component parts join other groups, or the central wave of one group may leave it to become one of the subsidiary waves of another group. (For example, if the objective of the consciousness of the moment be the construction of rhymes, loss, boss, toss, dross, coarse, may group themselves by similarity of sound around cross, whereas, were the objective changed, cross by similarity of ideas might become the central idea or wavelet of another group composed entirely of ideas dealing with religion.)

The wavelets in the further regions are more stable in their grouping. Those belonging to the stomach, for instance, are closely and permanently bound together, as are all those belonging to the knee-joint or the heart or the intestines. Waves that have to do with happenings in the past, especially with forgotten scenes and incidents, are also closely associated, and, when they migrate, move not singly, but as groups. This changing and rearranging is most active in the central part of the lake, is most inactive as we approach the borders.

Now assume that the whole sheet is in total darkness save that at or near the middle portion there is a light suspended from above, which illuminates a very small area. It is a mere pencil of light, capable of illuminating but one wave at a time, but it has the faculty of very rapid motion, and is thus capable of illuminating a good many waves in such quick succession that it produces the effect of having illuminated them almost simultaneously. This light represents the attention. To carry out the figure, we must imagine ourselves suspended above it and as being able to control its direction by our will. Just as the search-light of a battleship has a definite range beyond which the light does not reach, so the light of our attention can be projected over only a limited area of the sea of consciousness. All that lies outside this area, at any given moment, is, for that moment, sub-conscious—so that we speak of that portion of consciousness outside the range of the attention as the sub-consciousness and that portion which lies within the illuminated area as the consciousness; or, more accurately, the former is called the unaware consciousness, and the latter, the aware consciousness.

Bearing in mind the continual motion of the waves, we may picture them as coming single file and in groups, from the darkness into the light, and passing from the light out into the darkness again. One wave brings others in its train, and in the order of their associative values; and impelled by the object of the moment, we direct the light of our attention in a selective way upon the passing throng.

That sensations, real sensations, may make their impressions and become associated with other sensations without ever reaching the light of the attention—that, in other words, they can do this without our knowledge, is a factor of the greatest importance in understanding the hidden dynamics of our consciousness.

It is safe to say that there are a thousand times as many sensations recorded in the field of consciousness as are ever recognized, or, in other words, of which we have ever become aware. The fact of sub-conscious sensations, though an odd one at first sight, explains the many coordinate movements and automatic actions that without this explanation would remain mysteries.

Each family of waves may be said to be made up of two sub-groups; one of which, comprising the waves representing, for instance, the sensations of position, of vibration, and the deep muscle and tendon sensations, is a stable, stay-at-home cluster which normally always remains in the sub-consciousness. The other sub-group, which includes the sensations of touch, pain, and temperature, is more mobile, more loosely held together, and thus, any of its members are easily drawn from the family circle into the aware region. Any of these mobile sensations become very easily accentuated by the ordinary physical stimuli of the environment, and are thus constantly flashing in and out of the attentive region. Even without physical accentuation, one or more of them may be drawn to the attention, if one simply thinks of this or that part of one's body, and, consequently, at once becomes super-conscious of it.

Bearing this mechanism in mind, it is easy to see that sensations in this class, after being repeatedly picked out and dwelt upon by an otherwise idle attention, will form a most unwelcome habit of finding their way with greater and greater ease into the aware consciousness, and that consequently they will become exaggerated through repetition and over-attention. This process, in fact, plays an important part in the genesis of nervousness, where the sufferer becomes abnormally aware of many, one might almost say of all, of his sensations (and it also plays no small rôle in numerous other sorts of "nervousness").

There is another accident which may occur in the mental field which produces a similar result. Not only may the mobile sensations of the "touch" class, of which we normally may or may not be aware, become accentuated and exaggerated, but even those sensations of which we are normally never aware, namely, those belonging to the stable, sub-conscious group, may, under certain circumstances, reach the light of our attention. This they do by virtue of a process of disassociation, that is, by a breaking up of the normal arrangement of sensations in sub-groups and families. Thus, when a family of sensory waves becomes accentuated (although usually only the more mobile sub-group of the touch and pain class is affected), provided that the mental constitution be liable to disassociation, the lightly balanced associative values of a whole family may be upset. The result is that one or more sensations of the stay-at-home group, which should have remained quietly at home in the sub-consciousness, now disassociate themselves from this, their normal cluster, and promptly join the other sub-group of the family. They then assume the habits of their new companions and wander with them into the illuminated area. Thus, not only does the "touch" sensation become prominent, but it drags with it into the aware field one or more of its normally sub-conscious brothers. Here, of course, the latter literally "make a sensation." They wear the uniform, let us say, of the knee family and are therefore recognized as hailing from the knee country; but this is the only familiar characteristic they possess, and they are above everything fascinating to the attention because of the utter strangeness of all their other qualities. They are out of place—as startlingly out of place as fish out of water. The sensations are perfectly normal in themselves, but they are distinctly and markedly abnormal in their relative position in consciousness. Like deep-sea creatures suddenly hauled gasping to the surface, they are out of their natural element, the quiet sub-conscious regions, and are showing themselves in the utterly strange environment of the intensely active and brightly illuminated aware region. Of course they seem unnatural, undesirable; and furthermore, we treat them with fearful attention and respect, because they seem to signify that there is something very strange going on in the bodily region from which they emanate. The sufferer little realizes that their abnormality consists chiefly in mal-position, and not in intrinsic quality or significance.

Once having gained the *entrée*, the dislocated sensations in question very soon acquire the habit of calling with always greater frequency and familiarity. Naturally, the attention dwells with greater and greater intensity upon its strange guests, and the latter consequently swell to an enormous importance. Before long the secondary physical results make their appearance. The function over which the sensations in question formerly presided without let or hindrance now suffers over-stimulation or over-inhibition, as the case may be. The sensation, because of its abnormal activity and also because of its malposition in consciousness, has attracted more than its share of the attention and the latter consequently interferes with the nervous control of the function.

Then follow examples of bodily functions so disturbed. I will quote only two—fatigability and dyspepsia:

The candidate for this malady may have his attention drawn to his gastric sensations in any one of a variety of ways. An acute but passing indigestion, following some indiscretion of diet, may accentuate these feelings sufficiently to turn the trick. The reading of a patent medicine folder—which is usually a masterpiece of graphic description—may cause him to search his consciousness for the presence of any of the sensations described, and the search rarely fails to yield an ample regard. The sensations, however they may reach his attention, when once they have done so, are only too apt to become frequent visitors—this being almost inevitable, if he has been born with or has acquired the hypochondriacal tendency.

Beside these sensations, one or more of the sub-conscious stay-at-home group of the same family may join the procession. Whether this happens or not makes only a difference of degree in the result, and in either case, when once the sensations have engaged the attention sufficiently, the quiet autonomy is destroyed. The gastric functions are inhibited or stimulated, as the case may be, by the effect that the attention has had upon them in interfering with the quiet interchange of sensations and motor impulses which previously presided undisturbed over them in the outer-most sub-conscious regions. Consequently, too much or too little gastric juice is secreted, or the muscular action of the stomach is affected, and an actual chemical and mechanical disorder is established. The disturbance of gastric function then becomes responsible in itself for additional sensations which are abnormal not only in intensity, but also in quality. The latter do their part in further disturbing the harmonious automatism that should exist—worry does its share—and so the dance goes on.

Fatigability is one of the most prominent symptoms in "neurasthenia" and the one most often complained of. The latter fact probably has had no little effect in fixing the popular misnomer—*neurasthenic exhaustion*—upon this malady. As a matter of fact, fatigability is itself a misnomer, for the neurasthenic suffers not so much from true fatigue as from an overwhelming apprehensive *sense of fatigue*.

The genesis of this star in the galaxy of nervous symptoms is much the same as that of the preceding example (see dyspepsia). The patient, however, instead of suffering from the accentuation of merely a few sensations of the mobile class, or from intrusion into consciousness of a few others which normally should remain sub-conscious, becomes unduly aware of a great many sensations of both kinds and from nearly every part of the body. The attention is of the "ingrowing" type, sharpened to appreciate the slightest sensory changes, and thus that flood of sensations which is continuously pouring into the sub-consciousness in every one, and in normal people remaining there, is encouraged and indeed invited to overflow into the aware region on the slightest pretext. These sensations when they become conscious are vague, unnatural, disagreeable. They are not clean-cut and familiar, as are those of pain or heat or cold, but they form a jumbled mass,

without outline—without beginning or end. The sufferer does not experience the more or less comfortable, soporific sensations of the true fatigue that follows a 20-mile tramp, or comes as a natural result of a good day's work. On the contrary, the victim of fatigability feels as though his mind and body had been transformed into a seething mass of sensations and finds himself in a very agony of aching confusion. Quiet and rest, if he is still able to rest, will give only temporary relief, and for this very reason rest is sought more and more frequently and for ever more protracted periods, and with always less relief as the case progresses. The sufferer becomes more sensitive to the fatigue-like feelings—his attention becomes more exclusively occupied by his sensations, and consequently becomes more difficult to control. For this reason it actually requires more energy to hold the attention upon any outside matter and, therefore, in performing a given task, he suffers an actual and disproportionate mental fatigue, which adds its effect to the sensory turmoil. Furthermore, his sensations lead him into more and more pronounced physical indolence, varied only by absurdly heroic spurts of effort, and this very naturally results in the muscular weakness which always follows disuse, as well as in general sluggishness of nearly all of the mechanical and chemical functions of the body. Worry as to the outcome of the disorder and the emotional disturbances centering about self-pity are the links which complete the chain of the vicious cycle.

Only after a fair working knowledge of the human machine in order has been attained and the genesis of nervousness in general, as a disorder of the mechanism, is thoroughly understood, is reference made here and there to one or more of the particular symptoms complained of, but these are treated largely as illustrating the lessons, and as interesting only from this point of view, rather than as important items in themselves.

Next, the re-education deals directly with the abnormal condition and only through it indirectly with the more troublesome symptoms of the case, explaining their nature and genesis when possible. The condition which they signalize bears the emphasis and its cure is the main theme. Every effort is thus made to help the patient to evaluate his symptoms by rationalizing them and then giving him reasonable grounds upon which to shift his interest and attention away from feeling to action.

Such evidence as can be drawn from the patient's actual current experiences in following out his schedule is, of course, utilized to demonstrate the principles discussed and to make the theoretical re-education square with practical application.

From first to last, every effort must be made to change the point of view of the patient from that of morbid egocentricity to one of a healthful, positive purpose in life. Objectiveness must take the place of subjectiveness, ambition and courage must replace introspection and fear, and the patient must be taught that it is his right and duty to demand quiet and efficient service from his body and mind. He must realize that they constitute an apparatus which is the means, not the end, of life. The philosophy of acceptance must be accepted as the basis of rest and as the starting point of work, while the ideal of service must be made to crowd out the idea of self-preservation.

Re-education must include this revivifying of normal ideals, for the whole structure of physical and mental training would collapse without its object—normal life.

I have been struck in some instances—fortunately they have been few and I believe entirely the fault of my own technique—in which the labor of re-education and re-normalization of physical functions was wasted, and the patients soon slumped to their original subnormal condition because these necessary ideals were not forthcoming. The whole process, being thus without object, was foredoomed to failure.

The physical part of the treatment is carried out, as I have said before, according to a schedule (individual for each patient) in which the elements of exercise, work, recreation and rest are definitely stipulated, and as nearly as possible in the normal quantity and normal relative proportion.

As soon as the patients have acquired a good working modicum of self-control, and their physical condition has become satisfactory—with as little warning beforehand as possible—they are sent home on a trial trip, to apply their knowledge and the fruits of their practice to their own environment. The stay at home varies from two and three weeks to six months or more in length—according to the case and the environment. A return to Stockbridge for treatment usually follows the trial trip. It is in most cases short—a few days only—and usually consists in a critical review of the successes and failures in adjustment, and other experiences, brought out by the trial trip. The next home-going is apt to be permanent, but is often followed in six months or a year by another and final visit of a few days in Stockbridge.

In the milder cases, this series of trial trips is not necessary, but all cases, even these, are kept track of for 18 months or two years after discharge by means of reports written by the patients at regular intervals.

Results do not prove that an hypothesis is correct, but they are at least apt to be suggestive of its success or failure as a working hypothesis. Therefore, I beg to conclude this account of the Stockbridge treatment with a summary of results obtained. It is doubtful whether the treatment would have given better results if carried out in a sanatorium or hospital. The environmental conditions would certainly be less like those of a normal life.

The following table includes only cases of primary neurasthenia, and only those patients who have been discharged two years or over, and whose records are complete to date. Secondary neurasthenia, cases complicated by alcoholism, arteriosclerosis, tuberculosis, or other organic diseases, are omitted, as are also hysteria and the neurasthenia-like prodromal stages common to some of the organic psychoses.

It has proved difficult to obtain news from ex-patients (especially those who have been happily cured seem to be the slowest to answer our inquiries), and I have still to hear from some hundred or more.

RESULTS OF TREATMENT.

Of the 355 patients discharged two years ago or longer, whose records were complete at discharge, we know the present condition of 129. The following statistics of results apply, of course, only to this smaller number.

The standard by which the results are measured is as follows:

Improved means any distinct diminution of symptoms coupled with distinct increase in ability to live normally.

Much improved means ability to live a normal life and disappearance of at least 50% of the symptoms.

Cure means full ability to live a normal life without reappearance of symptoms and, if any emergencies and difficulties have arisen, ability to meet these in a normal way.

The statistics apply to the present condition of patients.

Patients discharged two years and over, 129.

No improvement	0.7%
Improved	15%
Much improved	36%
Cured	47% } 83%

Patients discharged three years and over, 91.

No improvement	1%
Improved	11%
Much improved	30%
Cured	57% } 87%

The higher percentage of cure in relation to "much improved," shown in the group of cases discharged longest, is suggestive of permanency in the results.

DURATION OF TREATMENT.

Average	4 weeks (aggregate).
Longest	6 months (aggregate).
	40% treated for 1 week or less.

DISCUSSION.

DR. BARKER: Nothing could be more interesting than to hear a man like Dr. Riggs, who has seen so many neurasthenic patients, talk about his own first-hand experience with them. I was glad to hear him speak of neurasthenic states as abnormal mental states, for I think all of us who have studied them carefully feel that the most striking features of the complaints of neurasthenics are of a psychiatric nature. Indeed, I think that much of the progress that is being made in the understanding of the nature of neurasthenia, and in its treatment, is due to the rapid development of psychology and of psychiatry. Of course, those of us who have nervous patients sent to us—"complete-nervous-breakdown" cases—realize very well that what is called "neurasthenia" is no unity. We receive under this label a great many different kinds of cases, and it is only by a very careful analysis of each case that we can come to a correct understanding of its nature. We find that many "neurasthenics" are really patients with beginning dementia paralytica; some are instances of beginning dementia præcox; a good many more belong in the manic-depressive group, and a large number of them represent beginning Graves' disease. I might enumerate a number of other conditions that we quickly learn to differentiate and to recognize. All of these patients may present symptoms that are usually called "neurasthenic symptoms."

The study of these patients, and especially of their inability to adapt themselves to their environment, demands, as Dr. Riggs has said, a knowledge of psychology and, especially, of personality. I think that we can learn much from the comparative psychologists, particularly as regards the fundamental instincts. I do not believe that personality can be adequately understood without a thorough knowledge of the instincts. We must take into account the instinct of flight with its emotion of fear, the instinct of

pugnacity with its emotion of anger, the parental instinct with the tender emotion that accompanies it, the reproductive instinct with its accompanying emotions, the instinct of repulsion and its emotion of disgust, the instinct of curiosity and its emotion of wonder, the instinct of self-abasement with its emotion of subjection, the instinct of self-assertion with its emotion of elation, etc. We must realize that each one of these instincts has a cognitive aspect, an affective aspect, and a conative aspect; out of these instincts, as elaborated, is compounded our whole psychic life, our thinking, feeling and striving. In animals, we can see the instincts in their simpler forms; in man, we can see how, on the top of the instincts, are built up sentiments, that is, groups of ideas, feelings, and strivings, in which a series of instincts may be combined into a larger unit and directed toward some object outside, as when one loves or hates a person or a country. Especially important is the growth of the self-regarding sentiment and its relation to "moral conduct." This self-regarding sentiment helps us to understand the influence of the social environment upon a developing personality—the effects of rewards and punishments, and of approval and disapproval. Finally, we are beginning to understand how some men rise to "a plane of conduct higher than that regulated by the approval and disapproval of their social circle," where they may at times stand up against public opinion and do what they believe to be right in defiance of it. Only after we understand how personalities are built up can we hope to understand the maladies of adjustment met with in the psychoneuroses. Our newer knowledge regarding the instincts and sentiments we owe especially to the comparative, the behavioristic, and the social psychologists, to men like Lloyd Morgan, Stout, Shand and MacDougall. The book by MacDougall on Social Psychology has interested me enormously, and I can recommend

it heartily to you for summer reading if you are not already familiar with it.

Dr. Riggs has spoken of Freud's ideas both favorably and unfavorably; and we like that kind of critical comment here. I feel as he does, that there is much that is good in Freud's method of psychoanalysis; it is often valuable, especially in extending the anamnesis. It seems to me that Freud has made a mistake in regarding as sexual in nature some emotions that comparative psychologists have shown us are not sexual emotions. For instance, I think Freud confuses the "tender emotion" of the parental instinct with the emotion of the sexual instinct. They are certainly sharply separable from one another, though in the sentiment of love of one person for another of the opposite sex, both of these emotions, along with others, may be concerned.

As to treatment by re-education, I concur in Dr. Riggs' view, that it is the best method of mental treatment we have for these patients. One must realize that the symptoms of the neurasthenic are not imaginary; their sufferings are real. They are just as real as those in typhoid or in measles. Sometimes the torture of these psychoneurotic states is as hard to bear as any physical pain to which people are ever subjected.

As to saying that neurasthenia is entirely mental in nature and origin, or that there is no physical basis for it, that takes one into rather deeper waters of discussion than I wish to enter just now. I, personally, believe that all the instincts have a physical basis, and that, in the building up of sentiments out of instincts, we have to think of the underlying physical or neural basis; and that this neural basis can be profoundly modified by environmental influences.

Dr. Riggs' paper touches upon many exceedingly interesting problems that might well be discussed, and I trust that others who follow me in the discussion will comment upon some of them.

THE GASTRO-INTESTINAL FINDINGS IN A CASE OF SPRUE, WITH A NOTE ON THE TREATMENT BASED ON THESE FINDINGS.

By THOMAS R. BROWN, M. D., Baltimore, Md.

The opportunities for studying sprue in this country are so rare that it seems justifiable to call attention to a case recently under our care, especially as intensive gastro-intestinal studies were made, from which certain conclusions of real interest could be drawn. Our work was entirely confined to observations in the digestive field, and did not touch upon what is perhaps the most interesting phase of the subject—the question of etiology. In this connection a great deal of work has been done in recent years, most observers concluding that the disease is parasitic in nature, as was originally suggested, I believe, by Galloway. Castellani at various times regarded a bacillus, a spirochete, and many yeasts, respectively, as causative factors, finally concluding that the condition was due to a yeast infection—106 of the 112 strains isolated by him being *Monilia*—and this is certainly the latest and probably the best view held as to the origin of sprue, although Justi and Beneke still hold that the cause is a rod-like bacillus with its primary seat in the intestine, the epithelium of the villi being especially involved. Ashford, who believes that the yeast—*Monilia*—is the cause, thinks that this fungus is found primarily in the mouth. Bahr,¹ after making very extensive researches on this subject, comes to the following conclusions:

1. Sprue is a specific disease of tropical and subtropical countries, though it is possible that cases originate in temperate zones.
2. It is a disease prevalent in Ceylon, especially amongst the Europeans, but, contrary to the opinion hitherto held, it may also occur in the native, irrespective of race or mode of life.
3. This fact, together with the occurrence of the disease in people closely associated, suggests a local influence or some communication from man to man.
4. Sprue is a variable disease; it may occur in a mild or in a particularly virulent form; and in common with many other serious diseases, it is sometimes liable to sudden remissions and latent periods.
5. There is evidence that the disease may occur in distinct and specific clinical forms, according to the portion of the alimentary canal attacked.
6. Researches on the composition of the stools point either to a complete absence or to an inefficiency of the intestinal digestive ferments.
7. Researches on the blood and urine are in favor of regarding sprue as an alimentary toxæmia.
8. The pathological findings are also in favor of this supposition and point to an infection with the thrush fungus (*Monilia albicans*) as being the organism concerned in its production; the balance of evidence I have collected on the whole would seem to be in favor of, rather than opposed to, this view.

Incidentally, all attempts to convey the disease in its clinical entity to animals, even monkeys, have failed, although Ash-

¹ Trans. Soc. Trop. Med., 1913, VII.

ford's experiments² in this connection are extremely suggestive. Some of his conclusions are:

1. The species of *Monilia* recovered by me from now nearly one hundred cases of sprue, and apparently a new species from careful cultural and morphological investigations, is a pathogen for current laboratory animals by hypodermic inoculation.
2. This species, which I will for the present call *Monilia X*, is ordinarily a low virulence organism.
3. When recovered from a patient with sprue and promptly injected into certain laboratory animals, it generally produces their rapid death from a mycotic septicemia.
4. When grown for a long time and frequently transplanted, the same organism which rapidly killed soon after isolation from a sprue patient seems to partially or completely lose its virulence.
5. This virulence may be recovered by passage through susceptible animals, and even reach such a point as to sicken or kill these animals by continued feeding.
6. Ordinarily an animal may not be killed by feeding *Monilia X* when first isolated from a sprue patient. Its virulence must be augmented by passage before uniform pathogenicity through feeding can be demonstrated.
7. In such animals the symptoms depend on the part of the intestinal tube most affected, in the portion in which these *Monilia* secure their first foothold.
8. A certain number of animals exposed by feeding, rapidly die of a *Monilia* septicemia believed by me to be due to a sudden primary pneumonia and secondary septicemia.
9. Animals escaping this fate succumb more slowly to what seems to be a toxin developed in the intestinal tract by a localization of these *Monilia*.
10. Feeding experiments have resulted in the production of a stomatitis on two occasions and in the appearance of severe and long-continued diarrhea on several occasions.
11. In one guinea-pig presenting a severe stomatitis, sections of the affected zone revealed *Monilia* in the midst of the muscular bundles below the subepithelial connective tissue. This may explain the tendency for sprue to recur after an apparent dietetic cure: the yeasts are starved out in the surface; the patient apparently recovers, and, later, the deep-lying roots of the mycelial layer push out toward the surface and re-establish a surface growth with its consequences and a relapse.

Our case occurred in a young woman of 24, married, with an absolutely negative family history and past history, and a normal digestive history except a tendency to constipation. She had lived in Porto Rico from March 13 to July 21, 1913, and from April, 1913, until the time she first came under our observation (July 20, 1914), had had a persistent diarrhoea—from three to twelve stools daily, associated with an extremely bad taste in the mouth, very suggestive of rotten eggs, and always worse when the diarrhoea was most marked, the stools being large, gray, and soft. On account of these gray stools, which had evidently been wrongly interpreted as evidence of gall-bladder disease, a cholecystostomy and incidentally an appendectomy had been done without any effect whatever upon the symptoms. While in Porto Rico the patient had drunk only boiled rain water, but had bathed in both salt and fresh water; she had had an eruption on her forearm suggesting mosquito bites, and had numerous ulcers in the mouth, especially on the lips. The case was definitely diagnosed as sprue, both in Porto Rico and in this country, by military physicians conversant

with the disease, and in the presence of her symptom-complex it seemed hard to arrive at any other diagnosis. When first seen by us she presented the picture of extreme emaciation, weighing less than 70 pounds, and giving a history of having lost 35 pounds during her illness. The thyroid, eyes, tonsils, teeth, heart and lungs were normal; the abdomen was negative except for a slight splanchoptosis; the pelvic organs were normal. The urine never showed anything pathological, and the Cammidge reaction was negative—the usual finding in sprue. The blood showed, R. B. C., 3,528,000; Hgb., 72%; W. B. C., 6200, with 56% of polymorphonuclear neutrophils, 31% of small and 11% of large mononuclears, and 1.5% of eosinophiles. During her month's stay in the hospital the temperature was never above 99° F.; the pulse rate varied from 70 to 94. The stools were very characteristic; they were of large size, soft, fermenting, gray or yellow-brown in color, but not especially foul, usually of acid reaction, and containing some undigested meat, starch, and fat, but no pus, blood, amœbæ, ova, or parasites. The sigmoidoscopic examination was negative. On admission the gastric contents showed a complete absence of hydrochloric acid, with a marked diminution of pepsin. The quantitative estimation of the pancreatic ferment, by the method described by us elsewhere,³ showed a complete absence of diastase, the ferment most satisfactorily studied, and also of trypsin and lipase, as far as we could determine. This absence of pancreatic ferments has been noted before in cases of sprue.

The treatment of the patient consisted in absolute rest, unlimited fresh air, oil rubs, a diet at first consisting exclusively of buttermilk, increased rapidly up to eight ounces every two hours, zwiebach, dry toast, and other simple food articles being gradually added, until after about six weeks the patient was on a fairly general mixed dietary, including the simple meats, green and starchy vegetables, the former in purée form, stewed fruits, fruit juices, butter and cream. Medically, she was given dilute hydrochloric acid and large doses of pancreatin—30 grains daily, together with calcium carbonate and a little tannic acid. We did not use emetin, as suggested by Schmitler. The patient improved very rapidly as regards weight, strength, and symptoms, the diarrhoea practically disappearing after a few days of treatment. When seen again in about four months' time she had gained a little over 20 pounds. The gastric contents then showed a small amount of free hydrochloric acid, but examination of the stools still showed a complete absence of the pancreatic ferments. When seen again, after another four months, she had gained altogether 35 pounds—in other words, her weight had become normal. She seemed absolutely well, had no digestive symptoms, and was on a general mixed dietary, the only foods she was unable to digest being corn, asparagus and oysters. The gastric analysis now showed normal amounts of hydrochloric acid and pepsin; incidentally, it may be said that the dosage of acid had been gradually reduced and finally discontinued without the appearance of any unpleasant symptoms. The stools,

² Am. Jour. Med. Sci., April, 1916, p. 520.

³ Johns Hopkins Hospital Bulletin, July, 1914.

however, still showed a complete absence of pancreatic ferment, and the patient herself had noted that, although stopping the muriatic acid produced no unpleasant symptoms, whenever the pancreatin was omitted for a few days there would always be a return of the diarrhœa with the characteristic gray, frothy stool. The patient was heard from very recently and is absolutely well except for the fact that she still has to take the pancreatin in order to prevent a return of the diarrhœa.

The diagnosis seems quite definite. Two of the diseases with which sprue is sometimes confused—pernicious anæmia and atrophy of the gastric mucosa—can certainly be eliminated, while too long a time—almost two years—has elapsed and the condition of the patient is far too good to warrant a suspicion of malignant disease of the pancreas.

This persistence of the pancreatic achylia is of sufficient interest to warrant the reporting of this case, and suggests that,

whatever the primary cause of the disease may be, certainly the appreciation of its effect upon the pancreatic secretion is of the utmost importance in the proper interpretation of the symptoms and signs in this disease.

The most striking features in our case were, first, the persistence of the complete absence of pancreatic secretions, not only during the stage of apparent illness, but even after the patient felt and seemed absolutely well; second, the essential rôle of the constant administration of pancreatin by mouth in the therapy of the disease; third, that whatever the cause of sprue, and at this writing it seems probable that it is due to an infection with monilia, the lack of pancreatic secretion seems persistent and fundamental, the absence of gastric juice variable and accidental; fourth, that as long as our patient still suffers from this pancreatic achylia she can in no wise be considered as cured, although clinically she is apparently well; and the ultimate outcome must still remain doubtful.

A UNIQUE CASE OF ATROPHY OF THE FATTY LAYER OF THE SKIN, PRECEDED BY THE INGESTION OF THE FAT BY LARGE PHAGOCYtic CELLS—MACROPHAGES.¹

By T. C. GILCHRIST, M. D., and L. W. KETRON, M. D.

(From the Dermatological Department of The Johns Hopkins University.)

The patient was a young girl, aged 8 years, who came of a good family. There was nothing of importance in the family history. She was a seven months' child, but there were no complications at birth.

In April, 1915, six months previous to our first examination, the mother had noticed a spot on the calf of the right leg. This was soon followed by lesions on the other leg and later on the thighs. The mother described them as "lumps under the skin which appeared to the naked eye as dimples." During this period of the development of the disease the patient's health was not very good. She had feverish attacks and loss of appetite on several occasions. There were no definite subjective symptoms. Various therapeutic measures were tried, but without any favorable results on the course of the disease.

Examination.—The patient was a rather underdeveloped, moderately nourished child, weighing 37 pounds. She was bright, rather serious-minded, and the expression on her face was that of a much older child.

The cutaneous changes were present only on the lower extremities, extending from the inguinal region to the ankles (Figs. 1 and 2).² The anterior and outer surfaces of the thighs were comparatively free, the condition being limited to the inner and posterior aspects. The greater portion of the legs was implicated except over the knees and directly over the anterior tibial surfaces. The most striking thing noted on general inspection was the distorted contour of the legs, visible

even with the stockings on, due to areas which were apparently sunken below the normal level of the skin.

Thighs.—The smallest lesion which could be seen was a pea-sized, irregular or round, bluish-tinted, slightly depressed macule, which was not sharply defined, but faded out gradually into the surrounding tissue. From these were formed larger, sunken, morphea-like patches, which were round, irregular or band-like, and attained to an area the size of 10 x 4 cm. The depth of the atrophy varied from something scarcely perceptible in the smaller lesions, to about 2 mm. in the larger ones. The skin over the atrophic areas looked entirely normal except for a dusky bluish color, which became more pronounced as the lesions increased in size. The edges were not raised above the normal level of the skin and arose from the atrophic center gradually or rather abruptly. There was no redness or scaling of the lesions.

On palpation of the affected area a new condition was found which was not manifest to the naked eye. This consisted of hard, sclerotic, freely movable, irregular or branching masses or strands, which varied in size from some which were barely palpable to others as large as a man's finger. These masses lay in the subcutaneous tissue and ran beneath the smaller atrophic macules and the apparently normal skin. They did not invade the tissues beneath the larger patches where the atrophy was complete, but in some cases were continuous with the edges of these patches. These subcutaneous strands extended for the most part down the inner sides of the thighs. The skin over the larger atrophic patches gave the normal elastic sensation. It was not hardened, was freely movable, and could be picked up between the fingers in the same manner

¹To appear simultaneously in *The Journal of Cutaneous Diseases*, October, 1916.

²We wish to express our thanks to Mr. Martin, of the Phipps Clinic, for his care in making our photographs.

as the normal skin over portions of the body where there is little or no fatty layer. The skin over the smaller macules could not be picked up in this manner, but was bound down, in many cases, to one of the deep infiltrations, giving a sensation similar to that found on palpation of a schirrous cancer of the breast. The edges of the large lesions were soft and usually passed abruptly into the normal skin; or, in some cases, they could be felt to be continuous with the subcutaneous infiltrations. At the edge of one of the atrophic patches two or three finger-nail-sized flat lumps could be felt, which had a cartilaginous hardness.

Legs.—On the legs the atrophic process had involved the greater portion of the posterior and lateral aspects. Here were seen palm-sized atrophic areas which spread with a smooth or serpiginous border. These had become confluent with other patches, leaving here and there islands or tongues of normal-looking tissue which felt hard or oedematous. The lesions on the legs differed from those on the thighs, in that they had indurated, pinkish-yellow or reddish edges which were covered by a few thin white scales. The skin over these lesions was elastic and was not bound down. It had a dusky bluish color, and beneath it the veins were distinctly visible. On the legs the subcutaneous infiltrations were not so distinct, because almost all the normal-looking tissue in this region felt like a brawny oedema or, in some cases, almost sclerodermatous tissue. There was some oedema with pitting at the lower border of the atrophy about the ankles. A slight elevation of temperature over the reddish edges of the lesions of the legs was perceptible.

Histological Examination.—Two pieces of tissue were excised for histological study and stained with the usual stains.

Preparation 1.—This tissue represented the smallest nodule which could be detected on the patient's thigh on deep palpation. Its existence gave no visible signs on the surface of the skin. It was hard to the touch and appeared to lie beneath the cutis.

The changes in the section were confined entirely to the fatty layer. The epidermis and the corium were unaffected. In the upper half of the fatty layer a small cellular nodule was seen, which was divided into lobules by the connective-tissue strands that passed down perpendicularly from the lower portion of the cutis (Fig. 3). This cellular infiltration, towards its center, had replaced most of the fatty tissue, but towards the periphery the fat spaces became more numerous and the infiltration gradually ended with prolongations, or isolated groups of cells, which lay between the strands of the fat framework. The new growth, towards the center, consisted of a cellular connective tissue within which numbers of plasma cells were scattered diffusely or lay in groups (Fig. 5). Towards the periphery, where numbers of fat spaces still remained, the infiltration was made up of fibroblasts, large endothelioid cells, small round cells, and scattered here and there, rather thickly in some areas, plasma cells and a few polymorphonuclear leucocytes. Besides these, there were other numerous and striking cells which were markedly conspicuous because of their arrangement and abundant protoplasm. These

lay mostly in the fat spaces, in some cases filling them; in others, lining them with gland-like regularity (Figs. 8 and 9). They were found mostly in the depths of the infiltration, but in the earliest stages of their formation isolated groups lying near blood vessels were occasionally seen at the extreme edge of the infiltration (Fig. 4). The nuclei of most of these cells were large, oval, irregular, or round, with a heavily staining chromatin network (Figs. 8 and 9). Some of them, however, were small, with a picnotic appearance, while others were larger, with a more faintly staining chromatin network. Mitotic figures were occasionally seen. The cells usually contained from one to three nuclei, but large giant cells were found with 50 or more nuclei (Fig. 6). The protoplasm was frequently two or three times the width of the nuclei, stained faintly with eosin and polychrome methylene-blue, and appeared as a fine foam-like network (Fig. 9). The contour of the cells varied with their location. When they completely filled the fat spaces, they were irregular or had a mosaic-like arrangement. If they surrounded the fat space, they were usually rectangular in shape, resembling the flattened cuboidal epithelium of a glandular structure (Figs. 8 and 9). In rare instances the fat spaces were surrounded by cells which did not have this foam-like protoplasm and suggested a cell of a leucocytic type (Fig. 4(b)).

In the comparatively normal fatty tissue surrounding the infiltration here and there could be seen small dilated blood vessels containing a number of polymorphonuclear leucocytes. Some of these vessels showed a proliferation of their endothelial lining and of the connective tissue surrounding them. Lying between the strands of the non-infiltrated fatty framework small groups of epithelioid or fibroblastic cells or plasma cells were occasionally seen.

Preparation 2.—This piece of tissue was excised from one of the large patches on the leg extending from the atrophic center through the elevated pinkish edge (Fig. 7). Here the changes were seen principally in the subcutaneous tissues. There was a slight scaling of the horny layer of the epidermis and a mild infiltration about the blood vessels in the cutis of the left half of the section. In the left third of the section (A), which corresponds to the elevated edge of the lesion, an infiltration was found in the fatty layer similar to that found in Preparation 1 (Fig. 7(d)). In following the section towards the right, the fatty tissue was seen to give way rather abruptly to a dense sclerotic tissue (B), within which were found, in nests or more or less diffusely scattered, large fibroblastic cells, large and small round cells and plasma cells. Newly forming and thickened blood vessels, showing endothelial proliferation, were seen. One small inclusion of fatty tissue was found, in which were seen the large cells described above (Fig. 10). Further towards the right, in an area corresponding to the atrophic center of the lesion, the sclerotic tissue became less prominent and very few changes were noted except the entire disappearance of the fatty layer (Fig. 7(c)).

A polychrome methylene-blue stain of both preparations showed no unusual increase of the mast cells. No change in the elastic tissue of the cutis was noted.

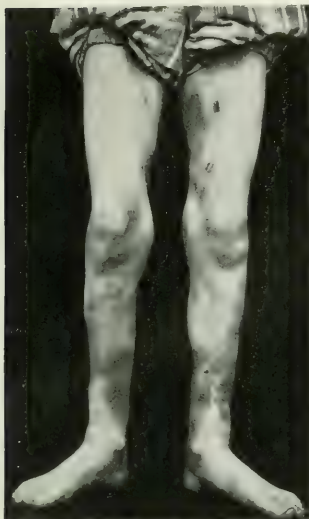


FIG. 1A.—Photograph, front view.



FIG. 1B.—Photograph, back view.



FIG. 2.—Photograph of a painting of the inner portion of the thigh and leg, by Prof. Max Broedel.

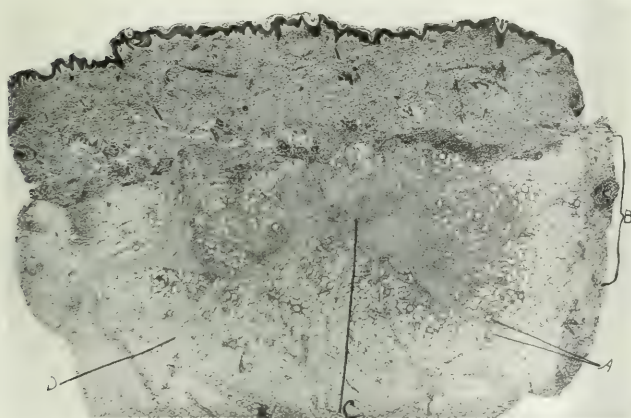


FIG. 3.—This represents the smallest lesion which could be palpated on the patient's thigh. The cellular infiltration is seen lying in the fatty layer *B* beneath a normal cutis. *A* is magnified in Fig. 4. *C* is magnified in Fig. 5. *D*, practically normal fat.

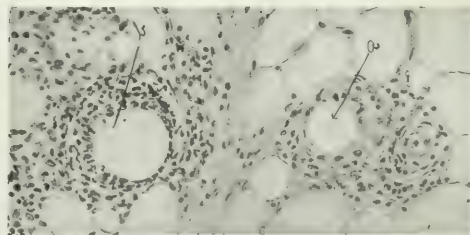


FIG. 4.—(Magnified portion *A* in Fig. 3.) At *a* is seen one of the earliest changes in the growth of the lesion seen in Fig. 3. Here is a small group of macrophages lying by the side of a blood vessel which is surrounded by normal-looking fatty tissue. At *b* is seen a fat globule surrounded by cells of a leucocytic type.

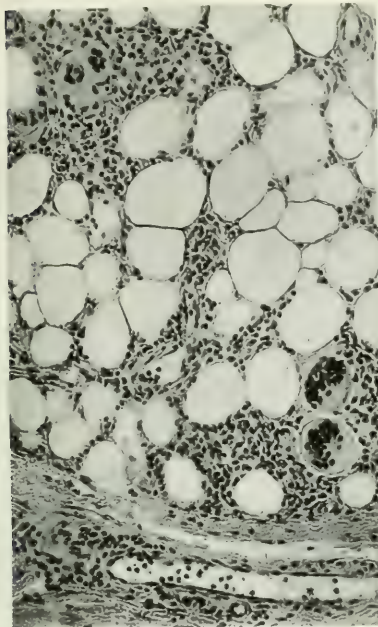


FIG. 6.—This section shows the large gland cells which are formed by the confluence of the macrophages.

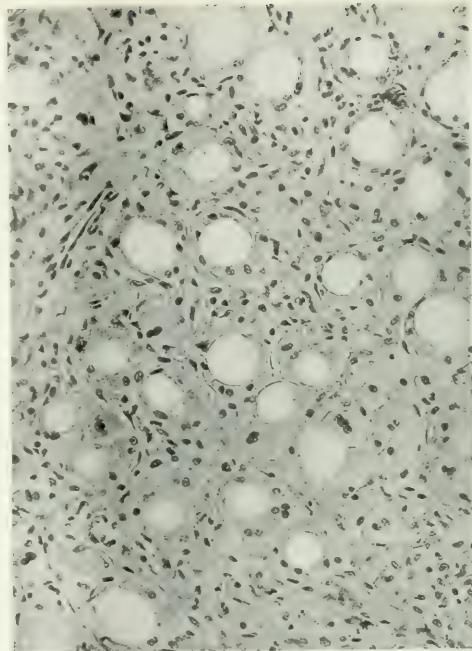


FIG. 8.—(Magnified portion *d* in Fig. 7.) Here is seen the arrangement of the large macrophages which fill the fat spaces or surround them with gland-like regularity.

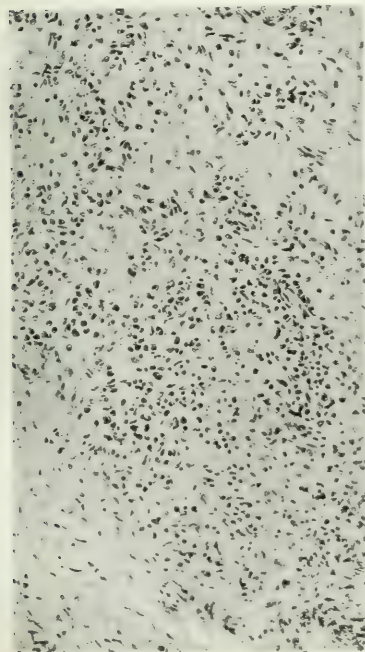


FIG. 5.—A large number of plasma cells, which were found towards the center of the infiltration shown in Fig. 3. (Magnified portion *c* in Fig. 3.)

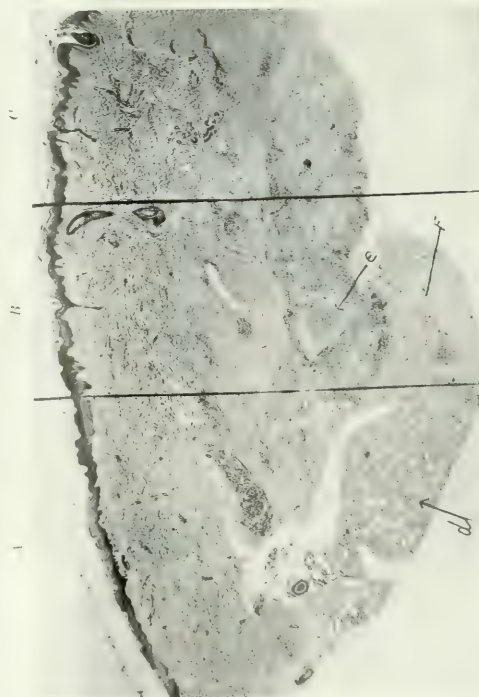


FIG. 7.—This section was taken through the edge of one of the large atrophic patches on the patient's leg. A represents the normal-looking, although slightly reddened, skin and shows the infiltration *d* in the fatty layer which is of a character similar to that seen in Fig. 3. B shows replacement of the infiltration in the fatty layer by sclerotic tissue. C represents the atrophic area in which the skin is practically normal except for the absence of the fatty layer. *d* is magnified in Fig. 8; *e* in Fig. 10 and *f* in Fig. 11.)

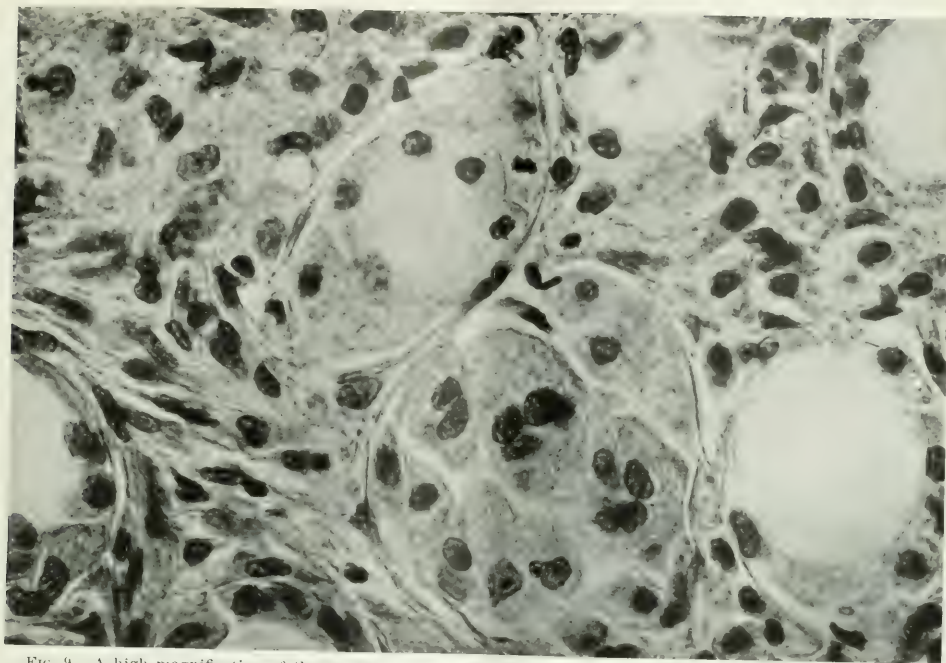


FIG. 9.—A high magnification of the macrophages showing their foam-like protoplasm. In the lower right-hand corner they are seen surrounding a fat space. Immediately to the left of this area they have completely filled the fat space.

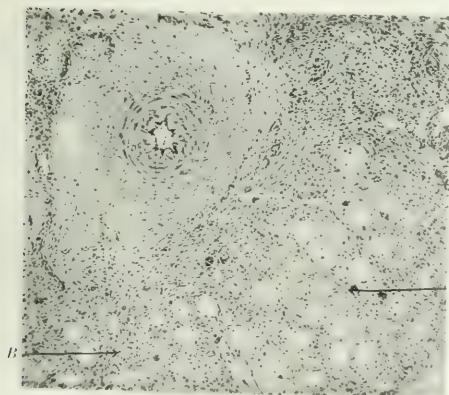


FIG. 10.—(Enlargement of Fig. 7, at *c*.) A small inclusion of fatty tissue surrounded by a richly cellular connective tissue. A degeneration of the tissue surrounding the artery is to be seen. Transition changes present from A to B.



FIG. 11.—Sclerotic tissue which has replaced the fatty layer, representing a stage later than that shown in Fig. 5. (Magnified portion *P* in Fig. 7.)

In order to study the fatty tissue of these preparations, some of the fresh tissue was stained with Soudan III. The fat spaces were seen to be filled with large, red-stained fat globules. The large single or multinucleated cells already described, which surrounded or replaced a fat globule, were filled with reddish-staining granules. These granules were also occasionally found in the cells lying in the infiltration at some distance from the fat.

The resemblance of these large cells to xanthoma cells, and the fact that the granules which they contained were shown by the Soudan III stain to be of a lipid nature, led also to investigations to determine the presence of cholesterol. Dr. Shipley, of the Anatomical Department, tested some of the fresh tissue with the polariscope, but no doubly refractive substances were found.

General Observations while the Patient Was in the Hospital.

—The patient was admitted to the Harriet Lane Home (Johns Hopkins Hospital) on October 28, 1915, about seven months after the beginning of the disease, and remained there during a period of about two months. Dr. Howland and other members of the hospital staff examined the patient, but nothing definitely pathological could be found with the exception of the skin lesions. Dr. C. M. Byrnes, who referred the case to one of us, found no abnormalities in the nervous system. There were no muscular disturbances and the glands of internal secretion were normal, as far as could be determined.

The Wassermann and von Pirquet reactions were negative. The urine contained no albumin, sugar or casts.

Dr. Shohle made a determination of the cholesterol of the patient's blood, but found no increase above the normal limits. (He examined at the same time the blood of a patient who showed numerous xanthoma lesions on the buttocks and elbows, and found a considerable increase in the cholesterol content.)

The temperature of the patient, which was 101° F. on entrance to the hospital, was subject to slight elevations at various times, but with no regularity. The white blood-cell count was 15,600, and the increase was in the polymorphonuclear elements.

From the time of admission the patient was about the ward and outside daily, except during the two attacks described below. She had a very good appetite and only complained, at various times, of indefinite pains in the legs. No internal medication was tried except potassium iodid, which was given for only a few days without benefit.

On December 9, about six weeks after admittance to the hospital, she had an acute attack of toxic erythema with macules and papules scattered over the body. This followed a period of constipation, and lasted three days. On December 17 she had a second attack of a toxic rash, associated with a rise in temperature and swelling of the joints. During this time the white blood-cell count was 26,000; a differential count showed, P. M. N., 86%; P. M. E., 1.6%; S. M., 8%; L. M., 1.2%; Trans., 3.2%; Hgb. (Sahli), 70%. This attack lasted also about three days, at the end of which time she was able to be up and about the ward.

On December 21 the patient was taken home with no definite change in the skin condition. She had gained two pounds in weight.

General Discussion.—The clinical course of the disease while the patient was in the hospital gave very little assistance as to the nature of the condition except that the slight, irregular rises in temperature, associated with the high leucocyte count, were suggestive of some chronic inflammatory process with suspicious exacerbations. The attacks of toxic erythema, we feel, might have had some connection with the course of the disease.

The histological findings show that the lesions in their development and evolution follow a definite course, which leads to the ultimate loss of the fatty layer without other permanent changes in the skin. The disease begins with the formation in the fatty layer of small nodules or strands, which are not perceptible to the naked eye, but are recognized only on deep palpation. These small nodules are made up of cells of a chronic inflammatory nature. The inflammatory process spreads only in the fatty layer, the fat itself being taken up in the cytoplasm of large phagocytic cells, which are very striking in appearance. After the fat has been removed the infiltration gives place to a fibrous tissue, the contraction of which leads to the formation of the small atrophic macules visible on the skin and which are bound down to the underlying masses. Later, as the lesions increase in size, this fibrous tissue is itself absorbed, leaving a soft, elastic skin which, owing to the loss of the fatty layer, has sunken down directly upon the muscular fascia. Since the edges of some of the lesions showed no induration, the sunken areas rising directly into the normal-feeling skin, the process must be subject to spontaneous arrest. The fact that the areas affected return to a practically normal state, except that the fatty layer is entirely lost, furnishes strong presumptive evidence that the rôle of the pathological process is to remove the fatty layer. This assumption is best supported if we further assume that the fat itself, through some chemical change, has been converted into a substance still of a fatty nature, but which acts as a foreign body in the tissues. The other possibility is to assume that the condition is an infective process, and that the invading organism has a special affinity for the fatty layer, changing the fat into some substance which acts as a foreign body. The difficulty here is that, if bacterial in origin, one would not expect the process to be so narrowly confined to the fatty layer and, also, would not look for such complete restitution of the areas affected after removal of the fat.

As to the nature of these phagocytic cells, they no doubt belong to what is classed as the "macrophage" group. This term, which was introduced by Metchnikoff, was at first rather indefinite in its application, but lately, especially as the result of the work of Evans³ with the acid azo dyes, it is now applied to a definite and important group of cells. When animals, which are normal or have been experimentally infected, are

³ Evans: "The Macrophages of Mammals." Amer. Jour. of Phys., 1915, XXXVI.

injected intravenously with these azo dyes, *e. g.*, trypan blue, the dye is stored in various portions of the body in the cytoplasm of certain large mononuclear cells, which have the power of taking up finely particulate matter. To this class of cells belong the Kupffer cells of the liver, which in malarial infections are filled with pigment, and the cells of the bronchial lymph glands, which in anthracosis contain pigment particles (coal dust). Other cells of endothelial origin, according to Evans, which have the power of taking up foreign bodies and which are found in the spleen, bone-marrow and the serous cavities, belong to this special group, as do, also, the clasmato-cytes of the skin and the foreign-body giant cells. It has been shown by Evans, Winternitz and Bowman* that the epithelioid cells and the giant cells of the miliary tubercle are pure colonies of these macrophages.

The similarity of the macrophages occurring in our case to xanthoma cells is striking. Anitschow[†] has shown, in the experimental production of xanthoma by introducing foreign bodies into the skin of animals fed on cholesterol, that large macrophages are first called forth by the introduction of the foreign bodies, and these are later transformed into the typical xanthoma cells because they take up the extravasated cholesterol which is present in excess in the blood. In xanthoma the foreign material is in the blood as a cholesterol-fatty-acid-ester, while in our case the foreign material is probably formed *in situ* from the normal fat.

In conclusion, we may say that, in the condition which we have described, there is a gradual progressive change in the fat of the subcutaneous tissue of the skin, due to some unknown

cause. This metamorphosed fat now acts as a foreign body in the tissues and calls forth a foreign-body inflammatory reaction. Macrophages, derived from the resting-tissue cells, the endothelium of the capillaries, and probably from the connective-tissue cells, now appear and phagocytose this changed fat, which they probably liberate in some soluble, inert form that can be excreted through the blood and lymph-channels.

After the fat has disappeared, this inflammatory reaction, its function accomplished, is replaced by a fibrous tissue which itself gradually disappears, leaving the skin practically normal with the exception of the absence of the fatty layer.

Note.—We saw the patient again in May, 1916, six months after our first observations. The changes observed were very interesting and corroborated and made stronger our previous convictions as to the nature of the pathological process. Two or three new depressions had appeared on the outside of the thighs, and those on the inner sides had increased in size. The atrophic process had practically covered the whole of the legs which now did not present the irregular contour observed at first, but looked and felt almost normal except for their extreme thinness, due to the absence of the fatty tissue. The induration, redness and œdema had disappeared, and the scar following the excision of our Preparation II, which was taken through the reddish, scaly, indurated edge of one of the large patches on the leg, was now surrounded by skin which on palpation gave a normal, elastic sensation. The mother said that the child had had another attack of a toxic rash, and at times still complained of pain in her ankles, but otherwise had been in very good health. There seemed, at this time, to be no interference with her muscular activity.

* Jour. Exper. Med., 1914, XIX.

† Arch. f. Dermat. u. Syph., 1914, CXX.

TETANUS FOLLOWING GUN-SHOT WOUNDS.

By J. A. C. COLSTON, M. D.

Tetanus, during the early part of the present European War, was a frequent and fatal complication, particularly of wounds caused by shell fragments. The prevalence of the infection was attributable to a number of environmental conditions, the most important of which was the highly fertilized soil of the northern and eastern departments of France, upon which the early sanguinary actions took place. In these regions practically all lacerated wounds were exposed to contamination with soil rich in tetanus bacilli and offered especially favorable conditions for their development. A further source of contamination lay in unsatisfactory transportation facilities. For example, some observers have claimed that the high percentage of tetanus infections among the French wounded, during the first month of the war, was due in no small part to the fact that many of these patients were carried, after being wounded, in cars which had been used for the transportation of horses and cattle to the fighting zone.

As soon as the prevalence of tetanus became evident, attention was called to the fact that practically none of the wounded at this time were given prophylactic doses of antitetanic serum,

as this was impossible as a routine procedure on account of the limited supply on hand and the large number of casualties. The importance of this measure was emphasized by Tuffier,¹ who was commissioned by the French war office to inspect the medical service of the French army. In his report before the Academy of Medicine of Paris on October 13, 1914, he placed especial emphasis on the necessity of the routine injection of all wounded men with antitetanic serum. Coincidentally with the introduction of this measure a remarkable reduction in the number of cases was noted.

Following the distribution of ample supplies of antitetanic serum by the French Sanitary Service to all dressing stations and receiving hospitals near the firing line, the wounded, practically without exception, received a prophylactic injection within 24 hours after injury, and a patient arriving at a base hospital without having had such an injection at present writing is a rarity. The isolated cases of tetanus that are still seen can almost all be explained by some omission or delay in the administration of the prophylactic dose.

Never before has the efficacy of antitetanic serum as a preventive of tetanus received proof on a larger scale, and when the records of the medical services of the belligerent armies become accessible, a comparison of the incidence of tetanus in the first two months of the war, when facilities for prophylactic injections were insufficient, with that in the succeeding months, when a thorough application of preventive inoculation was possible, will furnish the most certain proof of this simple and life-saving measure.

A considerable amount of literature dealing especially with the prevention and treatment of the great number of cases occurring during the early part of the war has already appeared. In addition to preventive inoculation, the importance of the early disinfection of the wound has been emphasized. Rogers,⁷ in some experiments conducted in 1905 upon rats, had already demonstrated the importance of this measure. He introduced street dust into multiple incised wounds; and of six animals so treated four died with tetanus, while of the six control animals whose wounds were irrigated with potassium permanganate solution, none developed symptoms. Unfortunately, in the majority of cases of gun-shot wounds such a procedure is inapplicable on account of the deep penetration of fragments of projectile and bits of clothing.

Fleming, in some interesting cultural studies of severe wounds, has furnished experimental proof of the efficacy of preventive inoculation. In an extensive series of anaerobic cultures from unselected cases he found 11 in which tetanus bacilli were recovered from badly lacerated and infected wounds. All of these patients had received antitetanic serum soon after the wound had been inflicted, and in only two had symptoms of tetanus appeared, these being mild and followed by a prompt recovery.

For practical purposes, three distinct types of the disease may be recognized clinically, according to the length of the incubation period. The acute fulminating type with onset of symptoms within three or four days after the infliction of the injury almost invariably results fatally, and treatment must necessarily be limited almost entirely to the relief of the distressing spasms. These cases are usually seen in field or evacuation hospitals, but one typical case of this type was observed in our service:

CASE 1.—Charles X., aged 26, was brought to the Sacré Coeur Hospital at Pau, one of 100 more or less seriously wounded patients. All the others had received prophylactic injections of serum before being placed on the hospital trains. The patient had been struck in the left hand about 60 hours before admission by a shell fragment, which had caused a compound fracture of the third and fourth metacarpal bones, with extensive laceration of the soft parts. He had refused the routine prophylactic injection at the evacuation hospital. Twelve hours after admission cramp-like pains developed in the left arm, rapidly followed by trismus. The patient died 36 hours later, after a typical course of opisthotonos, general tetanic spasms and firmly locked jaw. Intramuscular injections of antitetanic serum had no apparent effect.

The second and most frequent type is that in which the incubation period varies from five to 14 days. The mortality is between 60% and 70%, but it would seem that this could be

considerably reduced by an early recognition of the disease, prompt and thorough local measures and a careful choice of treatment. Five cases of this type were observed, four in the French Red Cross Hospital with three deaths, and one in the temporary hospital of the American Red Cross, treated with intraspinal injections of magnesium sulphate, with recovery.

CASE 2.—Alfred X., aged 40, was brought to the temporary hospital at the Palais d'Hiver on November 3, having been wounded 72 hours previously by shell fragments. He had received no antitetanic serum before admission, and none was given after his entrance, on account of the limited supply. Examination revealed an infected wound of entry on the posterior external aspect of the right buttock. There was no wound of exit. The roentgenograms showed a fragment of shell lying external to and about 5 cm. below the iliac crest. The wound did not drain well and signs of a localized infection developed, with a gradually rising temperature. On November 8, under chloroform anesthesia, the wound of entry was enlarged, an abscess evacuated and the projectile, with some fragments of clothing, removed. The wound was irrigated with salt solution and free drainage assured by means of a tube. The temperature promptly fell to normal and a satisfactory convalescence seemed assured.

On November 12, nine days after admission and 12 days after being wounded, the patient complained of cramp-like pains in the right leg and slight stiffness of the jaw. Ten cubic centimeters of antitetanic serum (Pasteur Institute) were injected intramuscularly. The next morning the stiffness of the jaw was more pronounced and tonic spasms of the leg were more frequent, with a general increased activity of the reflexes. The wound was opened widely, swabbed out with iodine and irrigated with potassium permanganate solution. No retention of pus was found. During the day three more intramuscular injections of serum were given, together with large doses of sodium bromide and chloral hydrate. During the next three days this treatment was continued, the patient receiving 30 cc. of the serum per day. The symptoms, however, became progressively worse and general tetanic convulsions and opisthotonos supervened. During the more severe spasms respiration ceased and cyanosis became pronounced. As these spasms were becoming more frequent and longer in duration, it was feared that a fatal result might occur at any time from spasm of the glottis. A lumbar puncture was done on November 16, chloroform being necessary to produce the necessary relaxation. Ten cubic centimeters of clear fluid under slight tension were withdrawn. Using the dosage of 1 cc. for each 25 pounds of body weight, as advised by Meltzer,⁸ 6 cc. of a 25% magnesium-sulphate solution was slowly injected, the head being kept slightly elevated to avoid involvement of the respiratory center. The respiration immediately became slow, shallow and irregular, but at no time was artificial respiration necessary. No appreciable effect was noticed on the heart. Several hours after the injection the temperature rose to 104° F. The patient remained deeply unconscious and completely relaxed during the next 36 hours. At the expiration of this time slight general contractions again appeared, but severe general spasms were absent, and, as respiration was unimpeded, no further injection was deemed advisable. Catheterization and nasal feeding were necessary for six days following the injection. The patient slowly recovered consciousness, was later able to take food by mouth, and regained control of the bladder and intestine. No contractions were noticed after the fifth day following the injection, and by the seventh day the rigidity of the jaw had completely disappeared. Stiffness in the right leg remained, however, for about six weeks, and convalescence was delayed by a somewhat severe bronchitis.

This case is unusual, in that a severe type of the disease developed after a rather long incubation period. The com-

plete relaxation obtained after the intraspinal injection carried the patient over what was apparently the critical period of his illness.

CASE 3.—Prosper X. was admitted to the French Red Cross Hospital five days after receiving a compound comminuted fracture of the first two metatarsal bones of the right foot. He had received no preventive injection, and no serum was obtainable after his admission to the hospital. The wound was foul and was complicated by an ascending lymphangitis, involving the foot and the lower two-thirds of the leg, which was treated by hot applications. Under this treatment combined with daily irrigations of the wound, the infection was successfully controlled until six days after admission, when cramp-like pains in the right leg with rigidity of the jaw appeared; the incubation period being thus 11 days. The wound was swabbed out with carbolic acid, and large doses of chloral hydrate were administered. The disease made rapid progress and the patient died in a severe convulsion 72 hours after the first symptoms were noticed.

CASE 4.—Henri X. was admitted to the French Red Cross Hospital five days after receiving penetrating wounds of the left heel and left shoulder. No preventive injection had been administered. On the day after admission a piece of shell with some comminuted fragments of the os calcis were removed under chloroform, and the wound was irrigated with salt solution. The condition of the wound improved steadily until six days after admission (11 days after the injury), when cramp-like pains in the left leg with rigidity of the jaw appeared, soon followed by general tetanic spasms. The patient was given daily intramuscular injections of 20 cc. of a 3% carbolic-acid solution combined with large doses of chloral. This treatment seemed to have little effect on the progress of the disease, and the patient died in general tetanic spasms five days after the appearance of the symptoms. No anti-tetanic serum was available for the treatment of this case.

CASE 5.—Jean X. was admitted to the French Red Cross Hospital with a compound fracture of the right tibia of six days' duration. No preventive inoculation had been given. The wound was badly infected and an ascending lymphangitis appeared and spread rapidly. Three days after admission the wound was opened widely under chloroform, numerous fragments of comminuted bone were removed, the cavity was irrigated with salt solution, and the whole leg put up in a large, hot, wet dressing. Under this treatment the lymphangitis subsided and the patient seemed to be making satisfactory progress until three days later (11 days after the injury), when he began to complain of cramps in the right leg. Rigidity of the jaw appeared on the next day, followed by spasms which subsequently became general. Following the appearance of the first symptoms the patient received daily intramuscular injections of 20 cc. of a 3% carbolic-acid solution. No antitetanic serum was given. The disease progressed slowly; the spasms became gradually more severe until death supervened from exhaustion, 11 days after the onset of the first symptoms.

CASE 6.—Mohammed X. was admitted to the French Red Cross Hospital with a comminuted fracture of the third and fourth metatarsals of the left foot, inflicted five days previously. No preventive injection had been administered. There were no untoward symptoms until six days after admission (11 days after the injury), when painful tonic spasms of the leg and slight rigidity of the jaw were noticed. Antitetanic serum (10 cc.) was immediately given. The slight general spasms continuing, a modified Pirogoff amputation of the foot was done, and daily intramuscular injections of 12 cc. of a 3% carbolic-acid solution were administered. For five days following the operation the patient was very ill with generalized spasms, opisthotonos and extreme rigidity of the jaw. The symptoms then became gradually less severe and entirely disappeared on the twelfth day.

This series of cases is, of course, too small to demonstrate the value of any method of treatment. The most striking result was obtained in Case 2, with the intraspinal administration of magnesium sulphate. This method was first introduced after the experimental studies of Meltzer and Auer. Blake¹ reported two cases in which the procedure was used successfully. Miller² reported another successful case and added a review of all cases treated by the method up to 1908. Falk³ reported favorable results in cases occurring during the Balkan War, but prefers the subcutaneous method of administration. Kocher⁴ emphasizes its value in severe cases, the treatment serving to control the tonic spasms until enough antibodies have been produced to successfully combat the toxins.

Stadler⁵ reported, previous to the war, two severe cases treated with magnesium sulphate, one of which terminated fatally. He collected from the literature 51 cases of various types treated by this method with a mortality of 35.5%. He contrasts these figures with those reported in large series of cases treated with serum or by other methods. The mortality of cases treated without serum was found, according to a compilation of many statistics, to be between 62% and 85%. The mortality of cases treated with serum was found to be between 39% and 64%. In cases with a long incubation period treated with magnesium sulphate the mortality was only 9%.

Eunike⁶ collected 27 cases treated with intraspinal injections of magnesium sulphate, the mortality being 33%. His own mortality in eight cases was 50%, but it must be remembered that tetanus from gun-shot wounds in war has a higher mortality than under ordinary conditions.

Kümmell,⁷ in a recent article, gives some interesting figures relative to the mortality from tetanus. Of 350 cases observed in hospitals near the front, 70% resulted fatally; while of those observed in base hospitals (*i. e.*, with a longer incubation period), 25% died. He recommends the magnesium sulphate treatment, but gives no statistics as to its value.

English writers give a somewhat higher mortality figure, those of Bruce⁸ being 78.2% for cases near the front, and 57.7% for cases occurring in British base hospitals. In an earlier report of a smaller series of cases, Keogh⁹ found a total mortality of 71.8%. Magnesium sulphate had been used only in very few of these cases, and usually by the subcutaneous method. English writers have obtained the best results with the intraspinal injections of serum.

From the reports of those who have used the intraspinal administration of magnesium sulphate, it would seem that this treatment is of great value in cases in which a fatal outcome is to be feared from spasm of the glottis or from exhaustion; and it is with the hope that this method will be more generally used in properly selected cases of the disease that these cases are reported.

I wish to express my thanks to Dr. Diriaut, surgeon-in-chief of the French Red Cross Hospital, through whose courtesy I was permitted to observe the cases under his care.

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GAS GANGRENE—ITS COURSE AND TREATMENT.*

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(From the laboratories of The Robert Walton Goelet Research Fund.)

The research conducted in this laboratory and published recently† has led to the conception of gas gangrene that is here presented. The treatment which this conception indicates is also suggested.

The condition usually meant by the term "gaseous gangrene" may be defined as *the death of an extensive mass of muscle due to the mechanical action of gas produced from a local focus by saprophytic bacteria*. The substances from which the gas is formed are chiefly the carbohydrate-containing tissues; hence, muscle is the tissue primarily involved. The organism is, with rare exceptions, *B. aerogenes capsulatus welchii* (*B. perfringens*).

In a previous paper we have discussed the stages through which a gaseous infection may pass.⁴ The first stage we have termed *dormant*; it represents the condition present in the majority of fresh wounds. We have reported finding the bacillus in 70% of all wounds examined bacteriologically at a general military hospital, and in a greater frequency in wounds examined within the first few days of injury.² In the first stage the bacteria are present in the remnants of dead muscle tissue. Gas may be apparent in the depths of the wound.

The second stage we have termed the *stage of gaseous distension*. This is marked by a gaseous infiltration of the healthy tissue, with retention of gas and consequent sustained pressure. A rapid increase in intramuscular pressure may quickly deprive the tissues of blood until the muscle appears as if it had been wrung dry of fluids, and the condition of gangrene supervenes.

* Presented at a meeting of The Johns Hopkins Hospital Medical Society, February 7, 1916.

† A detailed account of some of the points discussed here is to be found in the following articles:

1. "The Use of Quinine in the Treatment of Experimental Gaseous Gangrene," *Lancet*, 1915, Sept. 4, p. 538.
2. "The Use of Quinine Hydrochloride Solution as a Dressing for Infected Wounds," *British Medical Journal*, 1915, Dec. 25, p. 923.
3. "Factors Responsible for Gaseous Gangrene," *Lancet*, 1916, Jan. 15, p. 123.
4. "Observations on the Pathology and Bacteriology of Gas Gangrene," *Journal of Pathology and Bacteriology*, 1916, XX, 384-394.

The process may then pass into the *explosive stage* and progress rapidly, owing to the invasion of the gangrenous muscles by the bacilli. This, in turn, is accompanied or soon followed by the *stage of systemic toxæmia*, collapse, and death. In rare instances a stage of terminal bacteriæmia is reached.

From the standpoint of treatment, a study of the conditions which determine an extension of the process from Stage 1 to Stage 2 is clearly most important. It is against these conditions that treatment must be directed. After gaseous distension has occurred, the problem becomes immediately much more complicated. Many different factors suggested by others to account for the transition from the dormant stage into that of gaseous distension are insufficient to explain the sudden change:

1. It has been suggested that we are dealing with several different organisms. There appears, however, to be one distinct species—*B. aerogenes capsulatus*—which is responsible for nearly all the cases of gas gangrene.⁴ It is easily identified by its morphological and cultural characteristics. Other gas-producing organisms (with the exception of *B. adematidis maligni*) have not been observed to produce extensive lesions in the muscles. *B. adematidis maligni* is not often, if ever, the cause of extensive gaseous phlegmons, although it is not rare in the wound itself. The frequent occurrence of subcutaneous cedema associated with muscle distension is probably caused by the obstruction of the deep lymphatics and veins due to the increased intramuscular pressure.

2. It has been suggested that variation in virulence explains the different forms of infection seen in the patients. All strains of *B. aerogenes capsulatus* appear to be almost equally virulent for animals, and no relationship can be established between the severity of the human infection and the strain of the organism or its virulence for animals.²

3. It has been suggested that invasion of the blood is responsible for the malignant type of the disease. Metastasis, however, is almost unknown, and the presence of the bacillus in the blood is very rarely to be demonstrated during life.⁴

4. It has been suggested that absorption of soluble toxic products of the bacteria breaks down the natural immunity of the patient. The exotoxin is of only slight toxicity. Systemic toxic reactions from a local limited focus are slight. Symptoms of toxæmia occur only when a very large mass of

muscle tissue has been destroyed by the gas; then the putrefactive and autolytic, colliquative, necrosis induces rapid and profound toxic symptoms. The real action of the toxic principle is, we believe, that of converting healthy muscle tissue adjacent to the wound into a favorable medium for growth and gas production by the bacteria.²

5. It has been suggested that certain individuals fail to react to the infection, while others develop a prompt immunity. Active immunity must be established only very rarely, in any case, because the extension of the process, when it occurs, generally follows too quickly after the infection to allow time for the production of antibodies. Furthermore, as bacterial activity is limited chiefly to detached or necrotic tissues, no prompt systemic reaction is likely to result. No immune reactions could be demonstrated in the sera of animals or men who had recovered from the infection or had received prophylactic gas-bacillus vaccine. The bacillus is rarely phagocytosed in the wound. No increased resistance could be demonstrated even in animals that had recovered from a previous infection. Guinea-pigs show no variation in individual susceptibility to experimental inoculation.⁴

6. It has been frequently suggested that injury and thrombosis of important blood vessels cause the rapid invasion of the bacteria. Thrombosis of large vessels has been found in comparatively few of our cases coming to autopsy (3 out of 19), and was then probably a secondary result of the gaseous distension, and not the cause of the trouble. Ligation of the main artery to a limb probably brings about the death of the tissues through anæmia and allows of the rapid extension of the process in much the same manner as the gaseous distension.

7. It has been suggested that toxicity of the gas caused rapid necrosis of the tissues and the spread of the infection. We have shown the gas to be non-toxic for guinea-pigs.⁵

8. Frequently symbiotic relationship between the gas bacillus and certain other organisms has been credited with determining a malignant infection. There is no constant similarity between the flora of the various cases of gas gangrene.

The foregoing factors can probably be excluded as causative. Therefore, we must look to certain conditions in the wound to find the factors determining the development of a malignant condition.

In order for the infection in the dormant stage to result in gangrene in the stage of gaseous distension, two conditions seem to be necessary: first, a continuous production of gas in the wound; and, second, sustained pressure within a muscle mass following its infiltration and distension by the gas formed.

1. The continuous gas production depends on an adequate supply of dead muscle. The wound must provide this for the establishment of the saprophyte in an anaërobic medium favorable for its initial multiplication and the production of gas and toxin. Wounds made by fragments of shell and shrapnel with high velocity are especially likely to produce this condition by reason of their explosive effect on the semi-fluid muscle mass, in addition to the tearing action and the consequent separation of fragments of muscle from their blood supply. When bones are struck, the ragged splinters accomplish the result even more effectively.

The activity of the bacteria is limited almost invariably to muscle. Subcutaneous infections in animals are comparatively difficult to produce, and the invasion of the subcutaneous tissues by the bacteria is rare in man. When it occurs, it is usually in the region of the scalp or scrotum, where the skin is comparatively rich in muscle tissue. The area of subcutaneous crepitus is not, however, an indication of the extent of the infection, but is usually merely the evidence of the escape of gas from the muscles involved. It is generally after extensive damage to the deep muscle primarily invaded and after exudation into the subcutaneous tissue of the products of muscle degeneration that the bacteria are to be found growing and producing gas in this location.

2. Sustained pressure within a muscle mass depends on retention by intact muscle sheaths of the gas produced, and by the occlusion of the avenues of escape, due to the local swelling of the muscle fibers in response to the inflammatory reaction. The structure of muscle permits an easy infiltration of gas between and parallel to the fiber bundles. The same arrangement of fibers makes its escape correspondingly difficult except in a longitudinal direction, and this outlet is frequently blocked by the bulging of the fibers into the wound. This blocking of the avenues of escape for the gas is favored by various conditions. It is especially apt to occur when fracture of a long bone is present. This deprives the muscles of their splint, which would otherwise allow the longitudinal contraction of the cut fibers to tend to keep the wound open. When a fracture occurs, the contraction of the muscles closes the wound more firmly by allowing of lateral bulging. It follows, therefore, that an infected fracture is more easily drained of gas and pus when held in extension than before traction is applied.

TREATMENT.

If the above conclusions are correct and the transition from the first or dormant stage is dependent on the two factors—the presence of muscle debris and obstruction to the escape of the products of the bacteria growing in this debris—the treatment of such gaseous infection becomes clearly indicated. It consists in:

1. Prophylactic treatment during the dormant stage.
2. Treatment during the stage of gaseous distension.
3. Treatment of accomplished gangrene.

Prophylactic Treatment during the Dormant Stage.—This must include, first, an attempt toward the removal or destruction of the bacteria present in the wound and toward depriving them of their necessary soil, the dead muscle; second, the institution of precautionary measures against the occurrence of gaseous distension. Time is an important factor. The shorter the interval between injury and treatment, the more certain is a successful result. Thorough cleansing of the fresh wound is necessary, including the removal of all foreign bodies possible. (Under "foreign bodies" we include dirt, fragments of cloth, fragments of bone, and also any portions of muscle showing signs of necrosis.) Following the cleansing of the wound, the use of an antiseptic active against the gas bacillus is clearly indicated. For this purpose we have found a 1% solution of quinine hydrochloride to be effective clinically.* It

has proved experimentally, *in vitro* and in animals, to be much more active against the organism than any other solution we have tried.¹

In connection with the antiseptic treatment, in so far as it relates to the gas bacilli, it may be mentioned that certain solutions in common use show little bactericidal power against this organism *in vitro*. Potassium permanganate and hydrogen peroxide show no activity unless used in very large amounts, and then only temporarily inhibit the growth of the cultures. It is useless to attempt to produce an aerobic condition in a piece of necrotic tissue. Carbolic acid and hypochlorite solutions stimulate the growth of the organism *in vitro*, when present in weak concentrations. Furthermore, the bacillus grows readily in a medium containing as much as 2% of carbolic acid or 50% of Dakin's solution. The use of sugar solutions for dressings should be looked upon as dangerous, as they supply one of the necessary factors, a carbohydrate, for the active production of gas by the bacilli.

Oxygen, injected subcutaneously, cannot reach the focus of infection, which is in the muscle, and it probably serves only to increase the tension of the muscles and to interfere with the circulation of the parts. Moreover, it is sure to give an erroneous idea of the extent of the gas formed by the bacteria, and so confuse the clinical picture.

The use of anti-sera and vaccines is of doubtful value, if we consider the organism as a saprophyte, which has not invaded living tissues, and the damage done to the tissues as of a mechanical nature. It is also very uncertain that the muscle-toxic, hemolytic principle formed by the bacteria is a true soluble exotoxin for which an antitoxic serum can be produced.

The use of the cautery appears to have no logical basis, and late results of the treatment, as far as we have observed, seem merely to indicate that it furnishes foci for certain pyogenic infections of the tissue damaged by the heat.

In order to avoid the accident of gaseous distension, the following points must be considered: The wound should be kept as widely open as possible by means of a loose pack of gauze soaked in some wet dressing, preferably the quinine solution mentioned above. Any form of bandage or splint which increases pressure in the neighborhood of the wound or blocks the escape of gas, such as tight circular bandages, circular plaster casts, and so forth, must be avoided. The circular bandage bound tightly about a limb containing a fresh wound is undoubtedly frequently responsible for the development of gas gangrene. Wherever possible a gauze pad should be substituted and fixed in position with adhesive tape instead of with a circular bandage. Where fractures of the long bone are present, the limb should be put in extension as soon as possible, in order to keep the wound wide open. These points are especially important during the period of transportation of the wounded man.

Treatment during the Stage of Gaseous Distension.—Cases in this stage are frequently being subjected to a rapidly increasing intramuscular pressure. This pressure may speedily result in the production of the death of the muscle. Hence every effort should be made to recognize the first signs of distension and to relieve the pressure at the earliest possible

moment. The longitudinal arrangement of the fibers composing the muscle makes it difficult to release the gaseous pressure by longitudinal incisions, and it is necessary to make a larger number of such incisions than for the release of fluid. An attempt should be made to discover the focus of necrotic tissue where the active gas production is going on, and to remove the necrotic portions. The incisions should be dressed in a manner similar to that described for the wounds during the dormant stage. Irrigation may also be practiced, if desired, with one-tenth of 1% quinine hydrochloride solution in physiological saline.²

The Treatment of Gangrene.—If incisions into the muscle show a pale, dry, dull pink surface, and a consistency as if wrung dry of blood and lymph, the condition of gangrene is probably accomplished. The dead muscle is then a great menace to the patient, firstly, because it will speedily become an active source of gas production by the rapid invasion of the bacilli, and secondly, because the products of autolysis of a large mass of tissue may of themselves produce a profound toxæmia. Muscle in this condition will never regain its vitality. If the patient lives, it will be found to slough out in large fragments, sometimes as an entire muscle. Hence the treatment indicated is to remove the gangrenous tissue as quickly and as thoroughly as possible. This can usually be done only by amputation, if the process is in an extremity. No attempt should be made to cover the stump with skin flaps. The transverse section of the muscle fibers allows of free drainage of gas, and, unless extensive necrosis has occurred in the muscle tissues remaining, the process is frequently checked. The presence of subcutaneous crepitus above the possible limit of amputation, or even the presence of muscle involvement above that line, does not mean that the process will continue after the operation.

Summary.—We believe that the gas bacillus can be considered in its usual form as a pure saprophyte, and that the occurrence of gas gangrene should be regarded as the result of the mechanical accident of gaseous distension. We believe that, like tetanus, it is a preventable disease. The bacillus resembles that of tetanus in its frequent occurrence in cultivated soil, its need for anaerobic conditions which determine its saprophytic nature, and its need for a local focus of necrotic tissue in order to become a danger to its host. It differs from the tetanus bacillus in that with the latter the toxin is the active factor, whereas with the gas bacillus the mechanical action of the gas is the chief thing to be considered.

As in the case of tetanus, all fresh wounds should be considered as potentially malignant, and all available prophylactic measures should be applied routinely. We would suggest the routine use of quinine dressings as perhaps more nearly specific than any other antiseptic. Its use is especially indicated during the first few days after injury.

Special regard should be given to any factors which may compress the limb or interfere with free drainage of gas from the wound, particularly during the dangerous period of transportation.

I take pleasure in acknowledging my indebtedness to Dr. Joseph A. Blake for his kindness in criticising this paper.

THE PROGNOSTIC VALUE OF BLOOD CULTURES IN ERYSIPELAS.

By T. P. SPRUNT.

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In a series of cases of erysipelas during the past year in the City Hospital, we have been impressed with the value of routine blood cultures for the prognosis in this disease.

Five patients of the 34 showed a streptococcus bacteræmia. Of these, four died. The fifth had very few organisms in the blood, no other demonstrable complication, and recovered after a prolonged febrile course of 32 days, the longest of the series. The only other fatality occurred in a case in which a blood culture was unfortunately not made, but in which metastatic lesions suggest that a demonstrable bacteræmia existed. There was no death among the patients whose blood was sterile, though several complications were encountered, *e. g.*, suppuration, phlebitis, erysipelas migrans.

The prognosis in erysipelas is usually quite favorable. The mortality is given in most statistics as from 3 to 7 per cent in the facial type, and considerably higher in that complicating surgical conditions. Infancy, advanced age, alcoholism and complications are usually stated as indicative of a bad prognosis.

Concerning bacteræmia in erysipelas, the accepted teaching is that it is of rare occurrence.

Jochmann¹ reports only 16 instances in 463 cases, including 11 deaths and 5 recoveries. Anders² says: "A polymorphonuclear leucocytosis paralleling the violence of the infection occurs in this disease, but streptococci have not been found in the blood." Such statements in the most widely used reference books on Internal Medicine are so at variance with our experience in this small series that a note concerning these cases has been deemed of possible value.

In several cases we have seen patients enter the hospital with the typical history, symptoms and physical signs, with nothing to set them apart from other cases, but in which a positive blood culture has speedily given a clue to the gravity of the condition. Further, blood cultures stimulate continued and careful search throughout the subcutaneous tissues for deep-seated abscesses, which are not always easy of demonstration.

The method of making the culture was by means of the now generally familiar blood-agar mixture, the blood being obtained from an arm-vein in a sterile syringe and mixed with agar in the proportions of about one part of blood to five parts of melted agar at a temperature of 42° C. to 43° C., and poured at once into Petri dishes.

The number of colonies in each cubic centimeter of blood in the six positive cultures (five cases) was respectively 1500, 15, 4, 14, 2 and 4.

Among the 34 cases there were eight instances of suppuration, five in the subcutaneous tissues beneath the primary site of inflammation, only one of which was associated with bac-

teræmia. In the three with abscess formation at a distance from the erysipelatous area, bacteræmia was present in two; in the third no culture was made. Thrombosis, endocarditis, arthritis and relapse each occurred once, and bronchopneumonia twice.

The incidence of marked alcoholism in 11 cases and syphilis in 10, with the high average age of the patients, 47 years, may help to explain our rather high mortality of 14.7 per cent.

The leucocytosis was commensurate with the intensity of the infection; the average of 47 counts in non-fatal cases was 16,500, and of 11 counts in fatal cases, 26,250.

As a rule, there was a progressive rise in the leucocyte count in fatal cases and a gradual fall after the count on admission in non-fatal cases.

Abstracts of some of the more interesting cases are given below:

I. *Erysipelas (Facial); streptococcus bacteræmia; abscesses of scalp and buttock; acute aortic endocarditis; pulmonary tuberculosis.*

W. H., white, bricklayer, 57 years of age, was admitted March 28, 1916, and died April 24, 1916.

There had been no previous attack. Slight cough for several months without expectoration and occasional gastric discomfort were points of interest in the past history. He admitted the occasional use of alcohol.

The present illness began three days before admission with swelling around the left eye. By the next morning the swelling and redness had extended to the nose, and by that night had involved the right eye. The patient said he did not feel badly.

On examination, there was a typical facial erysipelas with a sharply defined border. The skin was hot, red, indurated and vesiculated over the nose, eyelids, cheeks and left ear. The fever was moderate, 102°-103° F., remittent; pulse, 100; W. B. C., 18,000.

March 30. The inflammation had extended to the right ear and to the angle of the jaw. The blood culture showed four colonies of streptococci per cubic centimeter of blood; and in the evening the patient became delirious. The Wassermann reaction was negative.

March 31. The delirium continued to such a degree that restraint was necessary to keep the patient in bed. The facial swelling had subsided and only the ears remained large and swollen. Collapse occurred during the night with recovery after strophanthin. W. B. C., 20,000.

For two days water and nourishment were administered through the stomach tube, after which the patient became sufficiently rational to make this procedure unnecessary. The lesions on the face disappeared with the exception of that in the skin over the right ear; the blood pressure rose to 120/65, and the temperature approached the normal.

April 4. The patient was quite weak and semi-delirious, and a small red area was noted on the right buttock. This enlarged, until on April 9 there were tenderness, heat and marked induration, deep seated, especially over the right gluteus maximus, and conforming somewhat in shape to that muscle. W. B. C., 25,000; the blood culture was sterile. Later the lesion over the buttock was opened and drained, as was a similar one which developed in the scalp. Pus from the former abscess showed Staphylococcus

¹ Jochmann: Mohr-Staehelin. Handbuch der inneren Medizin, 1911, Bd. 1, 726.

² Anders: Osler-McCrae. Modern Medicine, 1913, Vol. 1, 588.

ureus. There was a progressive downward course, high fever and death on April 24.

Autopsy 812. Anatomical diagnosis: Primary: Extensive necrosis of tissues over the sacrum; abscess of the right side of the scalp; acute vegetative endocarditis (aortic valve). Subsidiary: Proliferative tuberculosis, upper lobes; caseous bronchopneumonia, left lower.

II. *Erysipelas (Facial); streptococcus bacteremia; cellulitis, left leg; suppuration of scalp.*

H. E., colored stevedore, aged 33 years, was admitted April 20, 1916, and died May 2, 1916.

There had been no previous attack of erysipelas. Typhoid fever, tonsillitis, venereal sore without secondary manifestations, and the occasional drinking of gin were features of the past history.

The present illness had begun five days before with malaise and pain in the back and limbs. That night the patient had a chill, and the next day the face was swollen and tender.

The lesion was typical, involving both cheeks, the nose and the lids of both eyes; vesiculation was well marked. The temperature was remittent, reaching 104° and 105° F.; pulse, 100 to 120. The mucous membrane of the nose was red and swollen; the mouth showed extensive sordes, extreme pyorrhea and eroded teeth; W. B. C., 28,000.

April 22. The inflammation spread rapidly, involving both ears, the scalp, and practically closing the eyes. There were no signs of suppuration. The patient was delirious, talked at random, left his bed several times, and had hallucinations. A blood culture at this time was sterile.

April 24. W. B. C., 32,000; two days later, W. B. C., 30,000; the swelling of the face began to abate.

April 29. The erysipelas had almost disappeared, but there was no corresponding general improvement; a few coarse moist râles were heard at the left base.

May 1. W. B. C., 47,000. The patient was almost comatose, markedly asthenic with small, weak pulse. The blood culture showed 15 colonies of streptococci per cubic centimeter of blood. The cerebrospinal fluid was normal. A red, swollen area, discovered in the calf of the left leg was incised, and about an ounce of pus evacuated. Death occurred early next day.

Autopsy 820. Anatomical diagnosis: Primary: Erysipelas; abscesses of scalp and left leg; cloudy swelling of viscera; thrombosis in the right auricular appendage. Subsidiary: Chronic pleural adhesions; tuberculous bronchial lymphadenitis; bronchopneumonia.

III. *Erysipelas (Facial); streptococcus septicaemia; lobar pneumonia; syphilis (Wassermann); residual left hemiplegia; arteriosclerosis; hypertension.*

W. F., colored stevedore, aged 55 years, was admitted May 8, 1916, and died May 10, 1916.

There had been two previous admissions for facial erysipelas, on March 2 and on April 10, 1916, respectively. Both had been of the usual duration, with typical local signs, but with very slight general disturbance. During the second attack there was no fever and the leucocytes were 8600.

On this, the third admission, the temperature was high, 103.5° F.; the patient looked very ill; the respirations were rapid. There was a marked pyorrhea and some redness of the pharynx. Over the lungs there was no dullness, but many fine moist râles at the right base with harsh breath sounds and prolonged expiration. B. P., 150/100; W. B. C., 26,000.

May 9. Consolidation of right middle and upper part of right lower lobes. A blood culture showed 1500 colonies of streptococci per cubic centimeter of blood. The patient died on the next afternoon. No autopsy was permitted.

IV. *Erysipelas (Leg); streptococcus bacteremia; suppurative arthritis, right ankle; cerebrospinal syphilis.*

L. S., white, painter, aged 60, was admitted June 8, 1916, and died June 11, 1916.

He was semi-comatose and the history was not satisfactory. The temperature was 104°, the pulse 120; the respirations were of the Biot type. The face and extremities were very cyanotic; the pupils were normal in size and reaction; the general musculature was held rigidly; the neck was stiff and somewhat retracted. Numerous, short, involuntary muscular contractions occurred from time to time and any attempt at passive movements elicited protest. The right leg was deformed from an old fracture. About the right ankle, and extending upward half-way to the knee, the tissues were swollen, and the skin was hot and of a blotchy purplish red color without sharp line of demarcation. This area seemed especially tender.

On the day of admission the leucocytes were 8500, the spinal fluid showed no increase in cells, negative globulin reactions, but a positive Wassermann. The blood Wassermann was negative. Examination of the eye-grounds revealed a gray atrophy of the optic nerves. The blood culture contained 14 colonies of streptococci per cubic centimeter of blood.



FIG. 1. -Desquamation of skin following streptococcus bacteremia. (Case V.)

On the second day the leucocytes were 30,000. The next day suppuration was detected in the tissues about the right ankle, and two pus pockets were opened. About the same time, on the right arm at the site of a vena-puncture, and extending upward toward the axilla, a large, diffuse, soft, reddened swelling developed, and increased rapidly until death that afternoon. We considered this a metastatic infection due to extravasation of blood.

Autopsy 860. Anatomical diagnosis: Primary: Erysipelas (right leg); subcutaneous abscess extending into right ankle-joint; gangrene of skin (right arm). Subsidiary: Tuberculous bronchial lymphadenitis.

Central nervous system not examined.

V. *Erysipelas (Facial); streptococcus bacteremia; arteriosclerosis; syphilis (Wassermann); diffuse desquamation of the skin; recovery.*

A. J., colored orderly, 50 years of age, was admitted May 14, 1916, and became afebrile June 18, 1916.

The patient was a hospital orderly, but there was no erysipelas on the ward at that time. There had been no previous attack.

The present illness began the morning of admission and was accompanied by malaise, nausea and vomiting.

He was a well-developed, muscular man, with the characteristic butterfly pattern of facial erysipelas associated with nasal obstruc-

tion and a mucopurulent discharge. There was reddening of the pharynx, diffuse pyorrhœa and a considerable degree of dental caries. Some enlargement of the epitrochlear lymph nodes was noted, and a few fine râles were heard at the right base. The pulse was regular, the vessel wall was thick and tortuous. B. P., 120/85; W. B. C., 20,000. The temperature was remittent, reaching 102° to 103° F.

May 15. A blood culture revealed two colonies of *Strept. pyogenes* per cubic centimeter of blood. By the next day the redness and induration had practically disappeared from the nose and had advanced on both cheeks with marked swelling and tenderness over both parotid regions.

May 18. W. B. C., 18,200. Wassermann positive.

May 25. The inflammation had entirely subsided, leaving only a moderate desquamation of the skin. The temperature was still elevated, reaching 103° F. on that day. The patient made no complaint except that he was being bothered too much with needles and examinations. There was no enlargement of the cervical lymph nodes, no tenderness over the sinuses, mastoids or jugular veins; the eye-grounds and ear-drums were normal; there were some irregularity of the heart and dyspnea on the slightest exertion, but no cardiac murmurs. No lesion of the skin or subcutaneous tissue could be demonstrated anywhere. Rectal examination revealed nothing abnormal. A second blood culture showed four colonies of streptococci per cubic centimeter of blood.

During the next few days the patient ceased to protest against being kept in bed, slept or dozed lightly all the time, was easily

aroused, and quite irritable, and suspicious of all who approached him. No local signs were found after careful and thorough search.

May 28. W. B. C., 22,000. The temperature gradually declined, was very little elevated on May 31, and on June 1 was normal all day, with a leucocytosis of 24,000. The next day the fever appeared again, rising to 103° F. on June 5, when the leucocytes were 15,000.

On June 15, 16 and 17 the fever was only slight, the patient's mentality became quite clear, and he began a rapid and satisfactory convalescence, of which one interesting feature was the widespread desquamation of the superficial layer of the skin in thin flakes, 1 cm. or more in diameter. This was most marked over the neck, chest, upper arms and back, and closely resembled that seen after scarlet fever (Fig. 1).

The urine showed a trace of albumin and few casts. In none of our cases was there any evidence of acute nephritis.

Summary.—In our experience, streptococcus bacteræmia in erysipelas is not an unusual occurrence. Routine blood cultures should be made in all cases of erysipelas, since the information so obtained may be of value in prognosis. Repeated cultures are indicated in severe cases.

Our experience shows further that erysipelas may be treated in a general hospital with reasonably good facilities for isolation without any great danger of ward infection.

THE HISTORY OF THE DISCOVERY OF THE SECRETORY GLANDS AND THEIR FUNCTION.¹

By MORTIMER FRANK, B. S., M. D., Chicago, Ill.

The discovery of the circulation by William Harvey, in 1619, was the most important which has ever been made in medicine, and the source of most of the subsequent improvements. Supplemented with the discovery of the capillaries and that of the lymphatic system, the whole subject of anatomy and physiology was revolutionized, for now knowledge of the exchanges between the blood of the organs and tissues of the body became possible. Before Harvey's work, blood was supposed to be carried by the veins to the organs as well as from them, and the idea of the functions of the structures known as glands was based on this assumption. Hence, when the new theory came that in each organ blood flowed to it through the arteries alone, and through the organ from the arteries to the veins, and away from the organs along the veins, always in one direction, all these old views had to be changed.

Under the term "gland," the older writers included also many other organs, in fact, almost all the viscera. Of these, the three principal ones, the liver, heart and brain, were sources of blood, *spiritus vitalis* and *spiritus animalis*. The idea of "spirits" should have disappeared after the circulation of the blood was discovered, but it did not. Of the other organs, the spleen, lungs, kidneys, stomach, uterus, etc., each author placed them in this group according to his own definition of viscera which he regarded as sufficient after a logical

consideration of their supposed functions. Their point of view was that of gross anatomy, and not physiology like ours. Outside this group remained the glands which were called adenal, or in Latin *glandula*, the salivary glands, the thyroid, the lachrymal glands, as well as the pancreas. Included in this last classification were all such round-shaped bodies which are accepted to-day as lymphatic glands.

The forefathers of modern anatomy believed the glands to be well-defined parts of the body, but without any other connection with it than that afforded by means of veins, arteries and nerves. Neither salivary glands nor pancreas were known to possess ducts, and all these varied bodies were regarded from the same point of view. Nothing was known of their function except what was given by Galen: that when they were situated at the bifurcation of vessels, which is the case with the mesenteric glands, the parotid and the thymus, then their use was to support the veins and keep them in position, or, together with fat, help to fill out spaces and give form, as, for instance, the thyroid and lachrymal glands. They could also serve for emunctory purposes whereby excretory substances could be removed from the blood or adjacent tissues.

This was the point of view before the seventeenth century, when these organs became subjected to more exact research with the discovery of the excretory ducts.

The first step was taken by Johann Georg Wirsung, a Bavarian by birth, who discovered the pancreatic duct in 1642 while working as prosector for Vesling at Padua. Wirsung's

¹Read before a meeting of The Johns Hopkins Hospital Historical Club, April 6, 1916.

coworker, Moritz Hoffmann, claimed the discovery as his own, for in 1648 he had pointed it out in a turkey. A year after Wirsung described the duct in man he met with a tragic death by being shot as he was entering his house at night. The story states that a quarrel over the discovery of the duct was the cause of the murder, but it probably resulted from some private grudge.

In Vesling's *Syntagma Anatomicum*, it is described as an observation made by his pupil Wirsung, with reference to a canal (Fig. 1) which arises from the duodenum close to the mouth of the biliary duct and of its ramifications in the body of the pancreas. He says it is not difficult to recognize the duct, as it was often filled with a nearly colorless fluid, sharp in taste and like bile stained a silver color. He speaks of it having a valve which opens outwards and found it easy to pass a style through from the pancreas into the duodenum, but difficult to pass the style in the opposite direction. He says

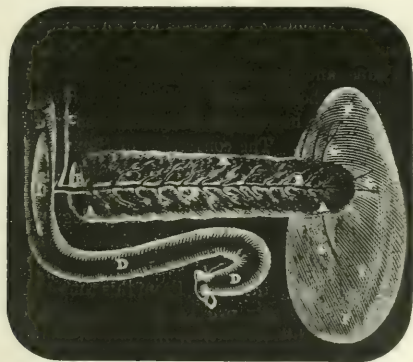


FIG. 1.

ORIGINAL FIGURE OF THE PANCREATIC DUCT FROM
VESLING'S SYNTAGMA.

that the duct is present in man and animals at all ages and could be neither an artery nor a vein, as it never contained blood.

The new fact so far as Wirsung was concerned remained barren, for he never followed up his discovery of the pancreatic duct by any study of the functions of the gland.

In 1654 Francis Glisson published his treatise on the liver, *Anatomia Hepatis*, and recognized its capsule which still bears his name. In that work he gave a very careful description of the anatomy of the organ, together with its form, position, weight, size, as well as its structure and function. He describes his method of tediously scraping away the parenchyma, after boiling for an hour in order to study the distribution of the vessels, as well as by maceration and by allowing the ants to eat away the soft parts (Fig. 2). It was by following the vessels uncovered in this manner from the portal fissure that he saw how the blood vessels and the branching bile duct were surrounded by a capsule of connective tissue, which we at the present day call Glisson's capsule. So far, however, as the intimate structure of the secreting substance of the liver is

concerned, he must have been ignorant, as he made apparently no use of the microscope. He believed the parenchyma to be the principal part of the liver and to exercise the purpose of a filter, a fact already stated by Vesalius. All other structures are simply subservient to it. It remained for Malpighi to show that the liver was a secreting gland, and consisted of lobules or acini. He already knew the difference between conglomerate glands, i. e., those with a duct as taught by Sylvius and his pupil, Steno, and conglobate or lymph glands. He thus inferred that the liver formed bile as the parotid forms saliva and is a conglomerate gland like the pancreas. Furthermore, since it is a feature of glands to possess an excretory duct, he concluded that the bile-duct is the proper excretory duct of the liver. Where Malpighi left the matter, there it remained with very little change until the past century, when chemical and physical methods were employed to solve the phenomena of living beings.

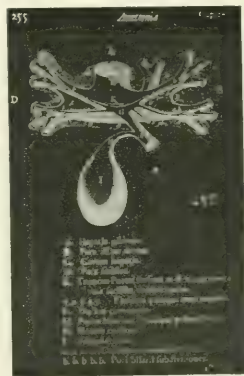


FIG. 2.

GLISSON'S ORIGINAL FIGURE SHOWING THE
HEPATIC STRUCTURES.

Shortly after Glisson's work there appeared in 1656, the *Adenographia* of Thomas Wharton. This publication marks an important epoch in anatomical discovery and deals not only with ductless glands, e. g., the thymus, but also with his own discovery of the duct of the submaxillary gland (Fig. 3A), the duct which has since borne his name. In this treatise he describes all those organs in the body which he called glands, their nerves, blood vessels and lymphatics. The results were originally given in his anatomical lectures at the College of Physicians in 1652. In the course of his dissections he noted the similarity between the pancreas and the submaxillary gland, namely, the lobulated form, the appearance and taste of the substance. This led Wharton to believe that perhaps the submaxillary gland had an excretory duct of its own and he made his dissections on the head of an ox where the larger dimensions gave a greater chance for success. He insists that real saliva and not mucus is discharged into the mouth through this duct and attached great importance to the nerves in the formation of the saliva, the fantastic action of the *sacculus nervosus*. He assumes that the saliva is a useful secretion in

various ways as it assists in the mastication of food, prevents a constant thirst and helps also to promote the "coctio," that is, the mixing of food in the stomach. Wharton paid scarcely any attention to the digestive uses of saliva and so failed to grasp the true significance of his important discovery. Its importance was seized upon later by Sylvius who regarded it as a type of fermentative juice and believed it to be the chief agent in bringing about the first stage of digestion.

Among all the anatomists of this century there is none more remarkable than the Dane, Niels Stensen, better known by his Latin name Steno. Born in Copenhagen in 1638, he studied medicine first in the university of his own town under the direction of Thomas Bartholin (1656), subsequently at Amsterdam under Blasius (1659), and later on under Sylvius at Leyden (1661). His studies, however, were not only medical, for he turned his versatile mind to other problems, and left an enduring mark of his genius on the science of geology as yet in its infancy.



FIG. 3.

- A. ORIGINAL FIGURES OF WHARTON'S DUCT OF THE SUBMAXILLARY GLAND OF A CALF.
B. STENO'S ORIGINAL FIGURE OF THE PAROTID DUCT AND LABIAL GLANDS OF A CALF.

Scarcely had Stensen, in 1661, taken his scalpel in hand when he discovered the duct of the parotid gland (Fig. 3B) which bears his name. This led to a dispute with Blasius, and Stensen went to Leyden to defend his claim to priority in a public debate with Jan Van Horne as president.

The discovery of the parotid duct was accidentally made while examining the vessels in the face of a sheep which Stensen had intended to use for dissecting the brain. A probe which was introduced into a canal that had been cut across struck with a sharp clink against the teeth and upon a closer examination it was discovered that one could go back from a natural opening on the mucous membrane of the cheek through a duct which led to the parotid gland. Sylvius found the duct in man. Later he investigated the duct of the sublingual gland, as well as those of the buccal glands, the alveolingual glands, the glands on the mucous membrane of the nose, palate and epiglottis and finally discovered the ducts of the lachrymal gland, and cleared up the problem of the secretion of tears.

Wharton had already discovered the submaxillary duct but pursued his discovery no further, while Stensen, who had learned from Sylvius the difference between the conglomerate glands, such as the pancreas and salivary glands, and the conglobate glands such as lymphatics, made use of the idea that the former were secretory glands and so must have ducts. At that time no one knew how saliva was formed and it was he who recognized that the material for the production of saliva or any other secretion is brought by the blood of the arteries to the substance of the gland. Owing to the inaccurate observations on the nature and functions of the glands, some thought that it came from the brain or the lymph and others from the papillæ of the tongue. It was Stensen who recognized the heart as muscular in its nature (1664) and a century later Haller called this work on muscle and gland, *De Musculis et Glandulis Observationum Specimen*, "a golden volume which contained the rich seed for new discoveries."

Disappointed at not receiving the appointment as professor of anatomy at Copenhagen, Stensen left for Paris and arrived there about 1664. From here he went to Italy, staying some time in Padua, and then going to Pisa in 1666. In Florence he joined the Catholic Church on the 2d of November, 1667, and ten years later he received the titular honor of Bishop of Titipolis in Greece. The conversion of Stensen to Catholicism in no way interfered with his studies, for after his conversion he occupied the chair of anatomy in Copenhagen and wrote his epoch-making work on the geological investigations of the stratifications of rock, fossils, etc. He stayed in his native town two years and in 1674 returned to Florence to work in his new calling, theology. From this time on he devoted himself to the duties of a priest and wearing himself out in constant labor for his faith, died in 1686 at the age of 48. The fruition of this brilliant existence, compounded of so many varied and significant elements, is to be found in the results attained by Stensen in his efforts to enrich anatomical knowledge and their influence on modern investigations. Some of his observations on the nature and functions of the glands are not exempt from error, but notwithstanding this, his work rendered invaluable service to the science, and prepared the way for the farther discoveries of anatomists of his and our own times.

In 1661, the same year that Stensen discovered the duct of the parotid gland, Malpighi described the true structure of the lung. Contrary to the earlier views that the lung was a porous, spongy and frothy organ, he found that it consisted of small air vesicles which were connected with the air passages. This observation made possible a theory of respiration, but the great fact was not yet clear. It was at this time, when examining the lung of a frog, that Malpighi discovered microscopically the capillary circulation, the missing link that made Harvey's work complete. Two centuries later Marshall Hall (1831) in a paper before the Royal Society, announced his discovery of the importance of the capillaries in metabolism of the tissues.

The use of the microscope by Malpighi made his discoveries possible and they were not only numerous and important, but

ranged over both the animal and vegetable kingdoms. Engaged in studies which were in their infancy in his time, yet his investigations in anatomy and physiology extended often to minuteness of detail. A contemporary of Harvey, Borelli, Stensen, Redi, Rudbeck, and Bartholin, Malpighi was born at Crevalcore, near Bologna, in 1628, the year in which Harvey published his book on the circulation of the blood. He entered, in 1645, the University of Bologna, and took his degree in medicine and philosophy in 1653. His thesis was devoted to the works of Hippocrates, whose thoughts he endeavored to revive, but his enthusiasm was only of temporary duration for he soon became interested in the new studies of anatomy and physiology.

When only 28 years old, he became professor in his own university, but in the same year accepted a more valuable appointment at Pisa on the invitation of Ferdinand II, Grand Duke of Tuscany, who created for him a special chair of theoretical medicine. Here at Pisa he made the acquaintance of Borelli, his senior by 20 years, and the two became close friends, Malpighi absorbing the new doctrines of mathematical-physical learning and Borelli on the other hand acquiring a knowledge of anatomy. Three years were thus spent at Pisa, teaching and learning, but owing to the climate Malpighi was obliged to resign on account of his health. Going back to Bologna he took up his former duties there, though after another short interval he was invited in 1662 to occupy the chair of medicine in Messina and accepted the offer. This post again was displeasing to him and once more after four years' absence he resumed his work in his native city and remained in it until 1691. On his way home from Sicily in 1666 he made a journey to Rome where he met and made friends with Stensen. In 1691 he was summoned to Rome by Pope Innocent XII to become his physician, died there in 1694 and was buried in Bologna.

The true scientific career of Malpighi began at Pisa where he had the good fortune to become the friend and colleague of Borelli and to him he first communicated most of his researches. In 1656, he examined the liver, spleen and kidney, and came to the conclusion that all these organs were to be considered as conglomerate glands. As to his views about the liver enough has been said already.

In his tract on the spleen he cleared up many indistinct theories. He gave a careful description of its structure, of its capsule, trabeculae and texture, and of its blood vessels. The trabeculae he at first thought were nervous in character, but soon recognized their contractile nature, and thus showed the spleen to be not a gland either conglomerate or conglobate, but a contractile vascular organ. He ascribed to the small white lymphoid infiltrations attached to the blood vessels which he found in the spleen and which still bear his name, Malpighian corpuscles, the rôle of glands, and as he did not find any excretory duct from them, he assumed that they emptied their products directly into the blood. To this day we still speculate as to the nature of the Malpighian corpuscle of the spleen, whether it has or has not a capsule, and what is its precise function.

The great achievement of Malpighi, however, relates to his researches into the structure of the kidney. In 1662, Lorenzo Bellini, a pupil of Borelli, in a little tract, *De Structura Renum*, described the straight tubes that still bear his name, but Malpighi went far beyond this and showed that the kidney consisted of masses of Bellini's tubules arranged in the form of pyramids, since known as the pyramids of Malpighi. He showed also how in each pyramid the tubules ended in orifices at the apex. But he did more than this, he saw the convoluted tubules and pointed out in injected preparations how many of these tubules began as inflated swellings or capsules and how these capsules contained a cluster of little blood vessels and so hung on to the small arteries like apples on a tree, and now called the Malpighian tufts. He was of the opinion that these were vascular in their nature and must play an important part in the secretion of urine. He conceived that from them the urine was secreted or derived and was given over by them into the tubular structure of the pyramids, to be discharged by the ureters and so to the bladder. Here he stopped and it remained for William Bowman and Carl Ludwig to work out the rest of the anatomic and physiologic problem. In his book on the viscera, *De Viscerum Structura*, etc., he not only believed the liver, spleen and kidney to be glandular in structure, but also the cortex of the brain.

He described the lingual papillae and regarded them as organs of taste and discovered the layer of epidermis called the rete mucosum or rete Malpighi in his honor. The point, however, which Malpighi emphasized in his investigation is not the layer which has retained his name, but the papillae, which he is inclined to assume are in connection with and possibly constitute or contain the nerve endings, and that consequently are the real organs for the sense of feeling and as in the tongue of taste.

He saw and described the openings of the sweat glands on the ends of the fingers but whether he saw the real body of the sweat glands is not clear from his description. The labors of Malpighi above recited are those likely to be of the greatest interest at this time, but they by no means cover the ground which he traversed. His famous researches on the silkworm including its development; his great work on embryology, *De Formatione Pulli in Ovo*, 1666, have become classic and like so many of Malpighi's other works were printed at the expense of the Royal Society.

An altogether different conception of glandular structure and physiology was advanced by Frederick Ruysch who was called to the chair of anatomy at Amsterdam while Malpighi was at Messina. A master in the technic of skillful injections, Ruysch thought that all glands are formed by the innumerable terminal branches of the blood vessels. Thus in the liver, that which was called parenchyma by Malpighi and regarded as glandular did not exist. Ruysch based his conclusions on injected specimens and believed that by scraping along the blood vessels according to the old methods the finer branches are destroyed, while on the other hand in a perfectly injected liver, one sees nothing else than the finer vascular branches. He made the blood vessels the agents instead of the aids of secretion.

Two years before the discovery by Stensen of the glands and ducts in the nasal mucous membrane, the old doctrine of catarrh from the brain was made the object of a virulent attack by Conrad Victor Schneider. He fills four thick quartos (*De Catarrhis*, 1660) with endless learning and elaboration to show that it was not the brain but the mucous membrane of the nose, which secreted the mucus discharged in disease. This highly important doctrine which seems to us now so simple and self-evident should be considered an important feature of the medical history of this period.

With the discoveries of the latter portions of the seventeenth century several familiar names are associated. Johann Conrad Peyer and Johann Conrad Brunner both born in the same year (1653) discovered the intestinal glands which bear their names.

The story of the discovery of the glands we now know by Peyer's name is interesting (Fig. 4). In 1667 he published



FIG. 4.

ORIGINAL FIGURE OF PEYER'S PATCHES IN THE SMALL AND LARGE INTESTINE.

his work *Exercitatio Anatomica Medica de Glandulis Intestinalium*, describing certain new glands which he says he discovered in 1673. He observed them first in the cat and stated that they are scattered over the intestine, some singly, and some in groups. He describes them as being provided each with a minute pore at its summit opening into the lumen of the intestine, from which can be pressed a little white sticky fluid. On account of the supposed duct which opened on the mucous surface, he regarded the individual small glands as secretory or conglomerate glands and not as lymphatic or conglobate. He assumes that the efficacy of the pancreatic juice becomes exhausted as the food mass descends from the duodenum, and that these glands secreted a digestive fluid which is most useful in the lower part of the small intestines. He discusses at some length in another part of the book the significance of the glands in diseases.

A few years later in 1687, Brunner described the glands in the duodenum that bear his name. In this year he became professor of medicine at Heidelberg and published his inaugural dissertation entitled, *Dissertatio Inauguralis de Glandulis Duodeni*, in which he writes about his discovery as follows: "I lowered an everted human stomach into warm water and

kept it there until it commenced to shrink. Then I separated the wrinkled membrane very carefully from the layer below as far as the pylorus, and when I had gone beyond it I was fortunate to find a gland not yet discovered and in a thick mass down to the mouth of the bile duct." He speaks of these glands as yielding a juice like that of the pancreas, and called them *pancreas secundarium*. He also described the glands in different animals. In 1682 before his call to Heidelberg he published his results on the pancreas, *Experimenta Nova Circa Pancreas*. In this he made known the removal of the part of the pancreas of a dog and succeeded in keeping the animal alive for a time. According to him the digestive functions were carried on normally and the dog was about as usual and well nourished. If this be so, Brunner contends that Sylvius and de Graaf were wrong in attributing the high importance which they did to the digestive powers of the pancreatic juice. In view of the connection between extirpation of the pancreas and glycosuria in our own day, made known by von Mering and Minkowski in 1889, it is interesting to note that in one dog he observed great thirst and frequent micturition and in another a ravenous appetite. The structures responsible for the production of glycosuria in extirpation of the pancreas have been found to be a group of specialized cells, called the islands of Langerhans. Thus it would appear that the pancreas possessed an internal secretion as well as a digestive function. As to Peyer's glands, Brunner was inclined to think that they only secreted a mere mucosity and that the real digestive intestinal agent was to be found in the glands he described.

The brilliant progress of anatomy and physiology during the seventeenth century laid the foundation for a still further advance in the eighteenth century. The names of many anatomists and physiologists of these times are familiar to all of us in that the name of the discoverer still clings to the various portions of the body.

Of the microscopic anatomists of the eighteenth century, one of the most prominent was Johann Lieberkühn who studied at Jena and Leyden and later became professor in Berlin. He was a master in the injection of vessels and the first to examine injected preparations microscopically. The glands that are associated with his name he described as round white bodies in the bottom of the follicles of the mucous membrane of the small intestine. He did not find them in the follicles of the large intestine although he was acquainted with the villi and follicles of the greater gut. He was not the first to have seen these glands, and the corpuscles which he found in the bottom of the follicles were probably masses of mucus, but the possibility that he saw Paneth's granular cells in the glands, present between the epithelial cells at the bottom of the crypts cannot be excluded.

Lieberkühn's crypts were found earlier by Pio Galeotti, a physician of Bologna who saw and described them in dogs and cats. In man he observed they are somewhat obscured by the villi. He used a microscope which had a magnification of ten times for his investigations. He made his preparations by putting ink on the mucous membrane and let it soak in, then looking at the inverted intestine by transmitted light, or

made sections and examined them under the microscope. Even before Galeotti's description, Malpighi and Pechlin are said to have seen these glands.

Many other distinguished names might be mentioned in connection with the history of the discovery of the glands but the time is short, and so only a word can be said of such men as Heinrich Meibom who published a work particularly referring to the glands of the eyelids (1666); William Cowper especially memorable for the two glands which have since borne his name (1694), though really discovered by Méry in 1684; Anton Nuck whose fame is associated with Nuck's glands and who studied excellently the doctrine of the glandular system (1685); Caspar Bartholin, Jr., the eminent anatomist whose reputation has been preserved to posterity by his researches and his association especially with the glands which bear his name (1675) though they had previously been seen by Duverney in the cow, and a host of others.

With respect to the phenomena of secretion by the glands, the view of the men about 1600 corresponded to the general physico-mechanical conception of nature. Later about 1757 the doctrine of irritability was established by Haller and made to rhyme with the theories of glandular function. In this year was published the first volume of his *Elementa Physiologia*, and it marks the beginning of modern physiology.

During the two centuries, the seventeenth and the eighteenth, physiological inquiries, as we have seen, swayed first in one direction and then in another to explain the cause of glandular secretion. It was left, however, for the nineteenth century to throw a new light on the whole subject, and it remained for Johannes Müller one of the greatest biologists of the last or any century to work out the finer histologic anatomy of the glandular tissues. In 1830 he published his monograph, *De Glandularum Secretionum Structura Penitiori*, and upheld the view of Ernest H. Weber that the acini of the gland are the direct continuation of the ducts and showed the exact relation of the capillaries to the acini themselves. The first researches as already stated were made by Malpighi in 1665. Ruysch attributed great importance to the blood vessels of the acini, and Haller endorsed his view. Müller's monograph ranges over all the glands and deals with those both of vertebrate and invertebrate animals.

The development of the cell-theory, one of the fundamental principles of modern science, explained for all times the phenomena of glandular activity. Two names are linked together in this connection, Matth. J. Schleiden and Theodor Schwann. The former proved that plant tissues are made up and developed from groups of cells (1838), and the latter made the almost contemporaneous discovery of animal cells (1839). Thus the discoveries and rational doctrines became in the course of time the accepted conception of organic life.

Closely associated with the anatomy and physiology of the foregoing glandular system is that of the ductless glands, the thyroid and thymus in the neck, the adrenal in the abdomen, and the pituitary in the head.

The thyroid gland was almost unknown to the ancients, and so far as is known antiquity possesses but one passage which

undoubtedly points to it. This occurs in a work, *De Voce*, which is attributed to Galen. In it he speaks of the glands of the larynx, "which are of a spongy nature, and the humor from them oozes out and trickles down, there being no necessity for ducts, and which have been created for the purpose of moistening and bathing all the parts of the larynx and the passages of the throat."

After Galen there is a long silence until Vesalius distinctly recognized its existence. In his *De Corporis Humani Fabrica*, 1543 (lib. vi, cap. iv) he states that "this dissection also shows two glands, one on each side of the root of the larynx, which are of large size and somewhat fungus, and nearly of the color of flesh, but rather darker and covered with many prominent vessels." Further on in the same chapter he suggests as a use for the thyroid, the moistening of the lumen of the trachea. In the second book (lib. ii, cap. xxi) he shows the thyroid in four of his illustrations of the larynx, and it appears as two round bodies, one on either side of the base. For a hundred years Vesalius' description of the organ was accepted. Up to the time that Thomas Wharton (*Adenographia*, 1656) gave it the name thyroid most writers either omitted referring to the gland, or spoke of it in the terms of the description given to it by Vesalius, "glandulas ad laryngis radicem adnatas." Wharton's was the first systematic account of the gland, and a whole chapter was devoted to it.

Giulio Casserius (*De Vocis Auditusque Organis Historia Anatomica*, 1600) accurately determined the position of the gland, and made some investigations as to the presence of an excretory duct, but concluded there was none. He regarded the thyroid as having an important part in relation to female beauty by filling out the sides of the neck.

Bartolommeo Eustachius (*Tabulae Anatomicae*, 1714) recognized that the two lobes are in effect one organ, and gave to the structure connecting the lateral lobes the name isthmus. Giovanni Battista Morgagni (*Adversaria Anatomica Omnia*, 1723) put an end for all time to the dispute as to the duality or singleness of the thyroid, but was of the opinion that there were minute ducts leading from the gland into the larynx. The question as to whether the thyroid possessed a duct or ducts was discussed with great animation until the beginning of the nineteenth century, when the opinion prevailed that there was no duct. With the appearance of Haller's work on physiology (1757-1766) the gross anatomy of the thyroid gland was well understood, but the case was quite otherwise in regard to the physiology of the organ. That the gland was relatively larger in women than in men was pointed out for the first time by Realdo Columbus (*Anatomica*, 1562). However, the first to definitely localize the thyroid as the anatomical seat of goiter was Fabricius ab Aquapendente (*Chirurgia*, 1619), although the Romans knew of the cervical enlargement in pregnancy (Catullus), and in endemic goiter (Juvenal), but there is no evidence to show that they associated this enlargement with the thyroid gland.

Various theories had been proposed to explain the function of the thyroid, and as a matter of fact much uncertainty still prevails at the present time. Most of the older anatomists

contented themselves with verbally repeating what others had said about its use. These for the most part regarded the thyroid as having an esthetic use in filling out the sides of the neck, or that the secretion served for the lubrication of the larynx, and so had an effect on the voice. There is probably no other gland in the body over which so many speculations have been made, and with regard to which such diverse opinions have been held, all of which were more or less fanciful.

The first to state the modern theory of the varied phenomena as applied to the glands of internal secretion was Théophile de Bordeu (1722-1776). In his *Analyse Médicinale du Sang*, published in the year of his death, he hit upon the doctrine that "not only each gland, but each organ of the body, is the workshop of specific substance or secretion which passes into the blood, and upon these secretions the physiologic integration of the body, as a whole, depends." One of the most interesting parts of Bordeu's theory is his observation of the effects of the testicular and ovarian secretions upon the organism, an important factor in the modern theory of the internal secretions, for nearly all these glands are in some way connected with the sexual characteristics of the individual.

The discovery of the glycogenic function of the liver by Claude Bernard, in 1849-57, was an achievement of no mean value. He observed that if an animal be fed on food containing neither starch nor sugar, or if it be starved, sugar is still found in the hepatic vein. The liver, therefore, besides forming bile, makes sugar, which it pours into the blood. Investigating further he washed out the blood vessels of an excised liver with water, until the washings gave no trace of sugar. On exposing the liver for a few hours to its normal temperature, and washing out its vessels again, there was an abundance of sugar. There was no denying the fact that animal cells did produce sugar. The next step was to isolate the substance from the liver, and in 1857 Bernard obtained glycogen in the pure state by his potash-alcohol process. (*Compt. rend. Soc. biol.*, 1855.) Thus he proved for all time that the liver formed an "internal secretion," which it poured into the blood, and not into a duct. It was this fact that established the theory of internal secretion as a working principle in physiology. About the same time he discovered on puncturing the floor of the fourth ventricle that he produced an artificial glycosuria (*Compt. rend. Soc. biol.*, 1849), or, as it is sometimes called, experimental diabetes (1849), which the later researches of Harvey Cushing and his associates believe to be a polyuria derived from the pituitary body.

Bernard's successor in the Collège de France, Brown-Séquard (1818-1894), by his researches on the adrenal and other glands, added much to our knowledge of this subject, and put the doctrine of internal secretion upon a firmer basis. In 1856, a year after Addison published his monograph on adrenal disease, Brown-Séquard (*Compt. rend. Acad. d. Sc.*, Paris) produced all the symptoms in different animals by the removal of the adrenal capsules. In the same year Moritz Schiff, of Frankfort-on-the-Main, found that excision of the thyroid gland in dogs was fatal, and many years later, in 1881, demonstrated that a small portion of the gland left behind,

or a portion implanted in the peritoneal cavity of the animal, or by the injection of thyroid juice into a vein or under the skin or by feeding by mouth with the raw thyroid gland, prevented the fatal symptoms of tremor, spasms and convulsions in thyroidectomized animals. This led to the successful treatment of myxedema by means of thyroid extract by Murray and Howitz, in 1892. The first description of this disease in man was by Gull, in 1873; and J. L. Reverdin, of Geneva, in 1892, showed that a complete excision of the thyroid in man produced an "operative myxedema." That cretinism, myxedema and operative myxedema were one and the same thing was stated by Sir Felix Semon in 1888 (*Tr. Clin. Soc.*, Lon., 1888). Exophthalmic goiter was described by Parry in 1786-1815, and by Flajani in 1833, Graves in 1835, and Basedow in 1840, but it was not until the year 1886 that Moebius attributed the train of symptoms to an excessive outpouring of the thyroidal secretion.

In 1896 Eugen Baumann discovered iodothylin in the body and suggested the relation of the thyroid gland to iodine metabolism, and in 1880 came the discovery by Tvar Sandström of the parathyroids (Upsala Läkaref., Förh.) which appear to have an influence upon calcium metabolism.

As has already been said, the pituitary body was regarded by Galen and the older anatomists as the source of mucous discharges of the nose, but was overthrown by Conrad Schneider in 1660. In 1778 Samuel Thomas von Soemmerring (*De Basi Encephali et Originibus Nervorum Cranio*) described the pituitary as the "hypophysis cerebri." It consists of two parts, an anterior glandular lobe (pars anterior) and a smaller posterior lobe (pars nervosa), the whole being connected with the floor of the fourth ventricle by means of an infundibulum. The anterior part secretes an eosinophile material which, according to Herring (1908), passes into the third ventricle, and thus into the cerebrospinal fluid. From the posterior part the active principles of the gland are obtained. Disease of the gland shows it to have a powerful influence on growth and metabolism. That the pituitary body is essential to the maintenance of life was proven by Nicholes Paulesco, of Bucharest, in 1908, who found that its removal was fatal to animals. He also discovered that the removal of the pars anterior was the same as the removal of the whole gland, but that excision of the pars nervosa is negative. This was corroborated by Harvey Cushing, who found, in addition, that partial removal of the anterior lobe in normal dogs produced obesity, with shrinkage of the external male genitalia. The results of experimental interference, however, are still somewhat in dispute. The same observer (1912) regards the state of acromegaly or gigantism as due to excessive activity, and that of obesity with eunuchoid changes as due to failure of pituitary secretion. Acromegalic giants have been known from remote antiquity, and John Hunter's famous chase after the body of the Irish giant O'Brien in 1783, showed that he saw the pathological importance of the specimen, which is shown in the background of Sir Joshua Reynolds' portrait of Hunter. Acromegaly was described by Saucerotte (1772), by Noel (1779), by Friedreich (1868), and others, and finally by Marie (1886), who gave the

disease its name, and in 1890 correlated it with the pituitary body.

Eustachius was the first to describe the adrenal gland, and it is placed, he says, "on the upper part of the kidney and adheres strongly to the diaphragm by a fold of peritoneum. Its substance and shape are similar to that of the kidney."

In a little monograph of 43 pages, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," published in 1855, Thomas Addison first recognized the characteristic symptoms now called Addison's disease, and it was this tract that induced Brown-Séquard in 1856 to reproduce the disease experimentally in animals by excising the adrenal capsules. The first investigations of the physiologic properties of adrenal extract were made by Oliver and Schaefer (1894), and by Abel of Johns Hopkins University in 1897, under the name of epinephrin. The active principle was isolated and prepared artificially by J. Takamine (1901).

The thymus was known to the Greeks, and was described by Rufus of Ephesus. As to the function of this organ, we are still very much in the dark. That it has some part in the normal growth cannot be doubted. It is large in early life and undergoes retrograde changes and becomes less and less as growth ceases. Its removal in young animals has been stated to cause retardation of growth, but Halnan and Marshall (1914) by careful experimentation on the removal of the gland in young guinea-pigs found no such effect on their growth.

The natural limits of this paper would be far exceeded by any detailed attempt to give an account of the remarkable fact that the identical effects of the ductless glands indicate that their functions are interrelated, and that they are in some peculiar way concerned in maintaining the equilibrium of the body. Nevertheless, one of the theories respecting the mechanism of this correlative status will be briefly alluded to.

Bayliss and Starling (1902) assumed that the chemical control of the body is accomplished by means of secretions, from the various organs and ductless glands serving as chemical messengers, whereby the products of a particular organ pass via the blood stream to distant parts of the body and produce a correlation upon the activities of those organs. To these chemical messengers they gave the name hormone. The only hormones of the ductless glands which have been isolated to date are adrenalin, iodothyron and pituitrin.

When we regard the rapid and marked progress which medicine has made during the past half a century, are we not fully justified in believing that progress in the future will be even more remarkable? There remains still a wide gap in our knowledge of the human body, and as we glance at the con-

dition of medicine in former times and reflect upon the superstition, ignorance and credulity that prevailed, we cannot help but be impressed with the vast debt we owe to our predecessors. We have learned much since their time, and are apt to make light of their labors in view of modern research, but if we could read the future we doubtless would find much to be ashamed of in our present knowledge.

DISCUSSION.

DR. HOWELL: As I listened to Dr. Frank's clear and comprehensive presentation of the development of our knowledge of the structure and functions of the glands, the thought that was uppermost in my mind was whether or not it was easier to make discoveries in the seventeenth century than it is to-day. I remember that some years ago, in a public address, a scientist asserted that in the early days of histological work it was only necessary to scratch a tissue with your thumb-nail to make a discovery. It seems as though the duct of Wharton, for example, should have been easy to find, but I suppose that it was not at that time. Will the problems that we are struggling with seem as easy to those who come after us as those of other days seem to us now? I really think that our task is more difficult. We cannot make so much use of the eye, or the eye sensitized and enlarged by the aid of the microscope. We have to depend to a larger extent upon the spiritual eye of the imagination, and that organ does not function in the same uniform and reliable fashion.

What has been the contribution of our times to this subject of the secretory organs? I suppose that the most important facts that we have added have been, in the first place, the demonstration of secretory nerve fibers to some of the glands, and in the second place, the discovery of the wonderful properties of the enzymes of the glands of external secretion and the hormones of the glands of internal secretion. But in regard to the processes controlling the formation of the secretions, I fear that we have made but little actual progress. We have attempted to apply to this problem the chemical and physical knowledge of the day, and it has not seemed to be sufficient. The processes of secretion are, in fact, processes of colloidal chemistry, and we must wait perhaps until this subject is more fully developed before we are able to penetrate further into the nature of the activities of the secreting cell.

I was much interested in Dr. Halsted's confessions in regard to the effect produced upon him by the discovery of the functions of the parathyroid gland. As I look back upon my own career as a student and worker in science and ask myself what single discovery affected me most, my impression is that I got the greatest thrill from Golgi's discovery of the wonderful structure of the nerve-cell. The news was brought to this country by Dr. Henry Donaldson, who had been working with Golgi. He had some beautiful specimens with him, but I recall that when he showed them to some of the older German histologists they were unconvinced and said you could not believe everything you saw with your eyes. To one brought up on the nerve network theory of Gerlach, those beautiful structures and the neuron conception opened up fascinating possibilities.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXVII is now in progress. The subscription price is \$2.00 per year.

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A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

BOOKS RECEIVED.

- The Art of Anaesthesia.* By Paluel J. Flagg, M.D. 136 illustrations. 1916. 8°. 341 pages. J. B. Lippincott Company, Philadelphia and London.
- The Mortality from Cancer Throughout the World.* By Frederick L. Hoffman, LL.D., F.S.S., F.A.S.A. 1915. 8°. 826 pages. The Prudential Press, Newark, New Jersey.
- Surgery in War.* By Alfred J. Hull, F.R.C.S. With a Preface by Sir Alfred Keogh, K.C.B., M.D. With 26 plates and 55 text figures. 1916. 12°. 390 pages. P. Blakiston's Son & Co., Philadelphia.
- Manual of Operative Surgery.* By John Fairbairn Binnie, A.M., C.M. (Aberdeen); F.A.C.S. Seventh edition, revised and enlarged. With 1597 illustrations, a number of which are printed in colors. 1916. 8°. 1363 pages. P. Blakiston's Son & Co., Philadelphia.
- American Association for Study and Prevention of Infant Mortality.* Transactions of the sixth annual meeting, 1915. 1916. 8°. 474 pages. Franklin Printing Company, Baltimore.
- A Text-Book of Fractures and Dislocations.* With Special Reference to Their Pathology Diagnosis and Treatment. By Kellogg Speed, S.B., M.D., F.A.C.S. Illustrated with 656 engravings. 1916. 8°. 888 pages. Lea & Febiger, Philadelphia and New York.
- Practical Physiological Chemistry.* A Book designed for Use in Courses in Practical Physiological Chemistry in Schools of Medicine and of Science. By Philip B. Hawk, M.S., Ph.D. Fifth edition, revised and enlarged. With two full-page plates of absorption spectra in colors, four additional full-page color plates and one hundred and seventy-two figures of which twelve are in colors. 1916. 8°. 638 pages. P. Blakiston's Son & Co., Philadelphia.
- Embryology, Anatomy, and Diseases of the Umbilicus, Together With Diseases of the Urachus.* By Thomas Stephen Cullen. Illustrated by Max Brödel. 1916. 4°. 680 pages. W. B. Saunders Company, Philadelphia and London.
- Gynecology.* By William P. Graves, A.B., M.D., F.A.C.S. With 303 half-tone and pen drawings by the author, and 122 microscopic drawings by Margaret Concree and Ruth Huestis. With 66 of the illustrations in colors. 1916. 4°. 770 pages. W. B. Saunders Company, Philadelphia and London.
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- United States Public Health Service.* Public Health Reports, Issued Weekly, Containing Information of the Current Prevalence of Disease, the Occurrence of Epidemics, Sanitary Legislation, and Related Subjects. Volume 30, Part 1, January-June, 1915. 8°. 1984 pages. Government Printing Office, Washington.
- Transactions of the College of Physicians of Philadelphia.* Third Series. Vol. xxxvii, 1915. 8°. 499 pages. Philadelphia.
- American Therapeutic Society.* Transactions of the American Therapeutic Society, Organized May 1, 1900. Incorporated July 7, 1904. Editor, A. Ernest Gallant. 1915. 8°. 135 pages.
- Department of Health of the City of New York.* Collected Studies from the Bureau of Laboratories, City of New York. Dr. William H. Park, Director. Volume viii, 1914-1915. 8°. 435 pages.
- The General Education Board.* Report of the Secretary, 1914-1915. 8°. 82 pages. New York City.
- The Kinetic Drive, Its Phenomena and Control.* By George W. Crile, M.D. Wesley M. Carpenter Lecture before The New York Academy of Medicine, 1915. Edited by Amy F. Rowland, B.S. Illustrated. 1916. 8°. 71 pages. W. B. Saunders Company, Philadelphia and London.
- International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by H. R. M. Landis, M.D. Volume ii. Twenty-sixth series. 1916. 8°. 311 pages. J. B. Lippincott Company, Philadelphia and London.
- Southern Surgical and Gynecological Association.* Transactions of the Southern Surgical and Gynecological Association. Edited by W. D. Haggard, M.D. Volume xxvii. 1915. 8°. 620 pages.
- Aseptic Surgical Technique.* With Especial Reference to Gynecological Operations, Together with Notes on the Technique Employed in Certain Supplementary Procedures. By Hunter Robb, M.D. 44 text figures and 24 plates. Fifth edition, revised. 1916. 12°. 292 pages. J. B. Lippincott Company, Philadelphia and London.
- Surgical and Gynecological Nursing.* By Edward Mason Parker, M.D., F.A.C.S., and Scott Dudley Breckinridge, M.D., F.A.C.S. With 134 illustrations in text. 1916. 8°. 425 pages. J. B. Lippincott Company, Philadelphia and London.
- Diseases of the Eye.* A Handbook of Ophthalmic Practice for Students and Practitioners. By George E. de Schweinitz, M.D., LL.D. (Univ. of Pa.). Eighth edition, reset with 386 illustrations and 7 colored plates. 1916. 8°. 754 pages. W. B. Saunders Company, Philadelphia and London.
- Collected Papers of the Mayo Clinic, Rochester, Minnesota.* Edited by Mrs. M. H. Mellish. Volume vii, 1915. 8°. 983 pages. W. B. Saunders Company, Philadelphia and London.
- Manual of Embryology.* By A. Melville Paterson, M.D., F.R.C.S. 1915. 12°. 391 pages. Oxford University Press. Henry Frowde; Hodder & Stoughton, London.
- United States Public Health Service.* Public Health Reports, Issued Weekly, Containing Information of the Current Prevalence of Disease, the Occurrence of Epidemics, Sanitary Legislation, and Related Subjects. Volume 30, Part 2, July-December, 1915. 8°. Government Printing Office, Washington.
- Collected Reprints.* By Thomas S. Cullen. Volume ii, 1904-1916. 4°. Baltimore, 1916.
- Carnegie Foundation for the Advancement of Teaching.* Tenth Annual Report of the President and of the Treasurer. 1915. 8°. 141 pages. New York City.
- Carnegie Foundation for the Advancement of Teaching.* A Comprehensive Plan of Insurance and Annuities for College Teachers. By Henry S. Pritchett. Bulletin Number Nine. 1916. 8°. 67 pages. New York City.

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ROENTGENOGRAPHY IN THE LOCALIZATION OF BRAIN TUMOR, BASED UPON A SERIES OF ONE HUNDRED CONSECUTIVE CASES.

By GEORGE J. HEUER AND WALTER E. DANDY.

(From the Surgical Service of The Johns Hopkins Hospital.)

Roentgenography was first applied to the study of intracranial tumors in 1897 by Obici and Bollici¹ and, almost simultaneously, by Oppenheim.² They attempted to show that brain tumors cast shadows in the roentgenogram, using in their studies preserved specimens placed in the skull with or without the brain. They experienced little difficulty in obtaining shadows under these artificial conditions, but failed in their efforts to demonstrate tumor-shadows in the roentgenograms from living subjects. Nevertheless, Oppenheim,³ although unsuccessful in his search for tumor-shadows, made an observation which indicated a more profitable field for study, namely, on the effects of brain tumor upon the skull; for, in 1889, he noted the destruction of the posterior clinoid processes of the sella turcica and made a correct diagnosis of an hypophyseal tumor from the roentgenogram.

Since the observations of Oppenheim a good deal of literature upon the X-ray diagnosis of brain tumor has appeared. For the most part it is widely scattered and consists of the citation of single cases showing tumor-shadows or deformations of the skull due to tumor; and, excepting the admirable monograph of Schüller,⁴ and the special studies of sellar deformations (Fuchs,⁵ Erdheim,⁶ Giordani,⁷ Jaugeas,⁸ Köhler,⁹ Fisher,¹⁰ and subsequent writers), conveys but little idea of the value of the X-ray in the localization of brain tumor. We have, therefore, studied the roentgenograms in 100 patients presenting clinical evidences of tumor, with the purpose of discovering

what abnormalities they show, and what value these abnormalities have in the focal diagnosis of brain tumor. We have found the presentation of the study difficult. In order to discuss variations from the normal, it is desirable to have in mind the X-ray picture of a normal skull. But, needless to say, perhaps no other bony structure presents so many apparently normal variations in shape and contour, not only of the skull as a whole, but of such individual structures as the sella turcica and the accessory sinuses, in the thickness and density of the bone and the prominence and distribution of its vascular supply, and in what are apparently pseudo-shadows, erosions or atrophic changes. The multiplicity of normal variations discourages the attempt to describe a normal skull as seen in the roentgenogram; and we shall merely indicate, in discussing the abnormalities due to tumor, the normal variations which may be confused with them. The difficulty of satisfactorily illustrating the text we have, in a measure, met by presenting with each untouched print a duplicate in which details lost in reproduction have been intensified. For this part of the work we are indebted to Mr. Brödel and Miss Norris; for the uniform excellence of the roentgenograms to Drs. Baetjer and Waters.

The present study, then, is based upon the first 100 patients with brain tumor who have come to the surgical service of Dr. Halsted since September, 1912. The statement, however, is not literally accurate, for we have included in the series patients with aneurism, pachymeningitis interna hemorrhagica,

grumma, tubercle, and arachnoiditis, who presented the clinical picture of tumor and whose roentgenograms showed abnormalities upon which we wish to comment. Ninety-six patients were operated upon, and through operation or subsequent autopsy we know the character and location of the lesion in 68.¹⁰ We have a roentgenogram, and with few exceptions a stereo-roentgenogram, of every patient. We have studied them rather from the viewpoint of the clinician than of the roentgenologist, using roentgenography as a laboratory aid in diagnosis in conjunction with a careful history and thorough neurological examination. Used in this way, abnormalities of the skull of significance to a roentgenologist must often be disregarded, because of historical and clinical data; and quite as frequently changes which of themselves are not impressive become significant when supported by physical signs. We may speak with some assurance of the roentgenological findings in the 68 patients in whom the location of the lesion is known; upon those of the remaining 32 patients we have hesitated to lay too much stress, although they have often been helpful in determining the diagnosis and operative procedures.

Regarded from the viewpoint of X-ray diagnosis, cerebral tumors may be roughly divided into three groups: (1) those which themselves cast a shadow in the X-ray plate; (2) those which, although casting no shadow, cause some deformation of the skull which we can recognize; and (3) those which give no evidence of their presence in the roentgenogram. The first group includes but few tumors, and in our experience only those that are bony or have undergone calcification, or, the uncalcified growths that have invaded the accessory sinuses. The majority of tumors belong to the second group, the roentgenograms showing not the tumor itself, but changes in the skull caused by its presence. These changes may be direct or local, caused by a tumor directly implicating a bony structure; or indirect, due to the pressure of the brain upon the interior of the skull caused by a tumor at a distance. We shall, then, discuss the X-ray manifestations of brain tumor under the following headings:

I. True tumor-shadows:

- (a) Uncalcified tumors.
- (b) Calcified tumors.

II. Changes in the skull due to tumor:

- (a) Changes in the skull due to general pressure:

1. Enlargement of the skull.
2. Separation of the cranial sutures.
3. General convolitional atrophy.
4. Destruction of the sella turcica.

- (b) Local changes in the skull:

1. Local hypertrophy of the skull.
2. Local expansion or enlargement without destruction.
3. Local atrophic changes.
4. Local convolitional atrophy.
5. Local sellar destruction.

- (c) Vascular changes in the skull due to tumor.

This is obviously only a working classification, and a combination of two or more of the above manifestations may be present in a given case.

I. TRUE TUMOR-SHADOWS.

(A) UNCALCIFIED TUMORS.

It has been the experience of those interested in the X-ray diagnosis of cerebral tumors that uncalcified growths rarely if ever cast a shadow in the X-ray plate; apparently this is to be explained by the fact that their tissue density, even though considerable as in the endothelioma, is not sufficiently greater than that of the surrounding brain. The first tumor-shadow reported (Church, 1899¹¹), and two subsequently described (Mills and Pfahler¹²), were of uncalcified cerebellar and cerebral growths; and, if undoubted, are exceptional. With a possible reservation to be mentioned, we have no evidence that an uncalcified cerebral or cerebellar tumor casts a shadow while within the intracranial chamber. When, however, an uncalcified tumor invades the sphenoidal sinus, it may become visible in the roentgenogram; for the invading tumor-tissue is sufficiently denser than the air normally contained in this sinus to cast a shadow. In the roentgenograms of three patients we consider the shadows due to uncalcified tumor-tissue invading the sphenoidal sinus (Fig. 1). Two are cases of hypophyseal tumor in which the tumor has partially destroyed the floor of the sella turcica and entered the sphenoidal sinus. The third is one of tumor (sarcoma) arising in the nasopharynx, which by extension has invaded the sphenoidal sinus and become intracranial, producing general pressure symptoms. No intracranial shadow, however, is visible. We have no examples of extension of tumor-tissue into other accessory sinuses.

The reservation made above refers to seven certified cases of hypophyseal and two of suprasellar tumor, in the roentgenograms of which are definite shadows in or immediately above the sella turcica (Table I, Fig. 2). Since the tissue removed

TABLE I. SHADOWS PROBABLY DUE TO AREAS OF CALCIFICATION IN TUMORS.

ASSUMPTION BASED UPON FOUR CASES IN WHICH HISTOLOGICAL SECTIONS OF TISSUE REMOVED AT OPERATION SHOW CALCIFICATION IN THE TUMOR.

X-Ray No.	Location of lesion.	Verified at	Diagnosis.
15996	Hypophysis. Operation.....		Adenoma.
21639	Suprasellar. Operation.....		Glioma.
26735			
29912			
23254	Hypophysis. Operation and autopsy ..		Cyst.
26435			
29000	Suprasellar. Autopsy.....		Glioma.
30810	Hypophysis. Operation.....		Adenoma.
33036	Hypophysis. Operation and autopsy ..		Cyst; Rathke's pouch.
34943	Hypophysis. Operation.....		Adenoma.
35312	Hypophysis. Operation and autopsy ..		Malignant adenoma.
35359	Hypophysis. Operation.....		Adenoma.

at operation has in four instances histologically shown calcification, we are inclined to consider the shadows in all to be due to areas of calcification. The point must be left unsettled for the present. The absence of similar shadows in the roentgenograms of our cases of certified temporal lobe tumor is against the possibility that they are due to uncalcified tissue.

Although these shadows in the sella turcica have little importance in the diagnosis of hypophyseal tumors, they may suggest glandular therapy in cases with a normal sella turcica and without neighborhood symptoms, but with glandular symptoms pointing to hypopituitarism, hypothyroidism, or their combination. A number of such cases, showing presumably extensive calcification of the hypophysis, have been observed, and a few have been definitely benefited by glandular therapy.

(B) CALCIFIED TUMORS (TABLE II, FIGS. 3-8).

True bony tumors (osteoma, osteosarcoma), or tumors which have undergone calcification or ossification, cast shadows in the X-ray plate that can be readily recognized; nevertheless, in a search of the literature we have found less than 20 recorded instances. We are aware that a number may have been over-

TABLE II. CALCIFIED OR BONY TUMORS CASTING SHADOWS IN THE X-RAY PLATE.

X-Ray No.	Location of lesion.	Verified	Diagnosis (Path.)
15517	Third ventricle. Ex-Only by X-Ray.		Glioma (?).
30238	Hemisphere; Postcen-At operation...		Osteosarcoma.
30263	tral.		
16456	Temporal fossa, left.. At autopsy....		Aneurism, internal carotid arteries.
19594	Hypophysis..... No.....		(?).
23529	Suprasellar. Third At operationCyst of Rathke's pouch.		
	ventricle. and autopsy. Calcification in cyst wall.		
35387	Chiasm and optic At operation...		Sarcoma.
	nerves.		

looked, for, as we have observed, the literature is widely scattered. Lichtheim¹² was one of the first to demonstrate the shadow of a calcified tumor—a calcified gumma. The shadow was not recognized until the autopsy had disclosed the character of the tumor. Fittig¹³ observed in the X-ray three calcified areas in the walls of cysts in an occipital-lobe glioma; Grunmach,¹⁴ a shadow due to a calcified tumor of the pineal gland; and Algyogi,¹⁵ a basal tumor with areas of calcification. Schüller¹⁶ reported an osteoma in the frontal region and two cerebral tumors; Klineberger,¹⁷ a tumor of the occipito-parietal region; Stieda,¹⁸ a calcified cysticercus; and Sträter,¹⁹ a calcified brain abscess, recognized after its disclosure at operation. Gottschalk²⁰ demonstrated a case of tumor-shadow before the German Roentgenological Society, but its reality was doubted by Holzknicht and Krause.²¹ Presumably, many of these pseudo-shadows have been erroneously diagnosed as true tumor-shadows.

The shadow cast by a calcified or bony growth varies with the nature of the tumor and the degree of bony or calcified change. It represents an area of increased density and is therefore of a lighter color than the surrounding negative. As commonly seen, the shadow of a solid tumor which has undergone extensive bony or calcified degeneration is quite dense but rarely of uniform density, owing to the scattered distribution of the bony or calcified areas. Its outlines may be quite definite; or

indefinite and marked by islands of calcified tissue. Although of great value in determining the presence and location of a tumor, the shadow may give no idea of its size; for, since the process of calcification is progressive, a large tumor may be represented by a small shadow if the process be early, and may be completely outlined if the process be advanced.

Quite a different appearance may be presented by those shadows due to areas of calcification in the walls of cysts, abscesses and aneurisms. In place of a solid shadow they may appear in the roentgenogram as a series of incomplete ring-shadows that mark the boundaries of a more or less spherical mass. Most typically this type of shadow is seen in the wall of an aneurism that has undergone calcification (Fig. 5).

The localized areas of diminished density appearing as dark shadows in many roentgenograms are not to be confused with true tumor-shadows. They may be due to atrophy of the skull over a tumor and indicate the location of an uncalcified growth.

In six cases in this series, definite shadows are present in the roentgenograms. Three are quite large; two representing solid tumors, one an aneurism of the internal carotid artery. Two are small shadows representing bony or calcified areas lying upon the posterior clinoid processes; they indicate the location of the lesions, but, as subsequent operation or autopsy showed, give no information as to the size. The sixth is due to the calcification of an hypophyseal tumor. Through the kindness of Dr. Barker we have had the opportunity of seeing a seventh, not included in this series, due apparently to calcification in a cysticercus in the pre-Rolandic area; for cysticerci were removed from the subcutaneous tissues.

Owing to the infrequency of tumor-shadows these cases are presented in some detail.

1. Surgical No. 30803. Fig. 3. The roentgenogram shows a dense irregular shadow consisting of a central mass, 4 x 5 cm. in diameter, from which radiating shadows extend in every direction, but principally anteriorly and inferiorly. It lies 3 cm. below the vault, 4.5 cm. above the sella, and 6 cm. posterior to the frontal bone. When viewed stereoscopically, the tumor-shadow is seen to be in the right hemisphere near the midline. The lower radiating shadows approach the sella turcica, cross the midline, and extend to the region of the optic nerve of the opposite side. There is no visible destruction of the sella turcica.

Clinical Note.—A white male, 26 years of age, was admitted to the hospital November 14, 1912, complaining of loss of vision. His past history is uninteresting. His present illness began in November, 1909, with the accidental discovery of loss of vision in his right eye. An examination at this time showed, in addition, considerable impairment of vision in his left eye. Within a month he was compelled to give up his position because of failing vision. He later returned to work, although there was no improvement in his sight, and continued working for at least another year. He has had periodic headaches, not especially severe, and never associated with nausea or vomiting.

Examination. Positive Findings.—A large, well-nourished, healthy-looking man; normal intelligence and speech; total blindness in the right eye and a complete temporal hemianopsia in the left; primary optic atrophy of both discs; exaggerated reflexes

upon the left side of the body. There are no outspoken signs referable to the hypophysis.

Operative Treatment.—None. In view of the X-ray findings an attempt to remove the tumor appeared unwise, and the patient refused a palliative decompression for the relief of headaches.

Comments.—The insidious onset and rather inconspicuous general pressure symptoms indicate that the tumor has been of exceptionally slow growth. There is a long history of headache, dating from childhood, but no apparent change in its character or severity. From the roentgenogram the cause of blindness seems undoubtedly due to pressure of the calcified tumor upon the chiasm. The diagnosis of a suprasellar lesion could undoubtedly have been made from the history and the characteristic eye changes; the extent of the growth, however, could be determined only from the roentgenogram.

2. Surgical No. 31295. Figs. 4 and 4a. The shadow measures approximately 6 x 5 cm. in diameter, is dense, irregular in outline and presents minute isolated shadows at its periphery. Viewed stereoscopically, this calcified tumor seems to arise from the skull over the left parietal region and to extend well into the intracranial chamber.

Clinical Note.—A white, married female, aged 20, was admitted to the hospital June 9, 1915, with the complaint of headache and the presence of a tumor on her head. For five years she had noticed a tumor over the left parietal region, beginning as a small nodule and gradually growing until it measured roughly 7.5 x 6 cm. in diameter. A year ago she began to have headaches, general in character, but often frontal. These have increased in frequency and severity and on one or two occasions been associated with vomiting. There have been no other symptoms.

Examination. Positive Findings.—A bony prominence over the left temporo-parietal region measuring 7.5 x 6 cm. in diameter; double choked disc of 3 to 4 diopters; slight facial weakness on the right side; slightly increased reflexes upon the right side.

Operative Treatment.—A bone flap was outlined, the extent of which was guided largely by the roentgenogram. On lifting the bone the tumor was found tightly adherent to it and to the underlying dura. Therefore, before any attempt to elevate the bone flap, a dural flap was made. After elevation of the bone and dural flaps, the tumor, subsequently diagnosed as an osteosarcoma, was easily lifted out of a depression in the cortex. There were no adhesions between the surface of the tumor and the piaarachnoid of the hemisphere. The entire bone and dural flaps were removed. The dural defect was covered with a free transplant of fascia. The patient made a satisfactory recovery.

Comments.—A case in which the focal diagnosis could have been made perhaps from the prominence over the temporo-parietal region. The roentgenogram, however, showed us the character and size of the tumor and prevented us from making a mistake we had previously made of interpreting the protrusion as due to an osteoma of the skull.

3. Surgical No. 31628. Figs. 5 and 5a. Considered as a whole, the shadow in this case is of an entirely different character from the two preceding. It consists of a series of incomplete ring-shadows rather than a single solid shadow. There are seven distinct shadows in an area measuring 8 cm. antero-posteriorly and 5.7 cm. vertically, the series of shadows lying in the temporal fossa and encroaching upon the region of the sella turcica. The autopsy showed that the shadows in the roentgenogram represented areas of calcification in the wall of an aneurism of the internal carotid artery.

Clinical Note.—A white, married male, aged 28, was admitted to the hospital March 3, 1913. (He had two subsequent admissions, in October, 1913, and July, 1914.) Complaint, headache and failing vision. The present illness began over four years before this first admission with dimness of vision in his left eye. Three months later he began to have violent headaches associated with vomiting. They continued for six months; then gradually disappeared. He had at this time, exophthalmos with blindness of the left eye, and internal strabismus. Then for a period of four years he was free from headaches and able to perform his duties as a government telegraph operator. After this period of comparative health, vision became impaired in his right eye, and, fearing blindness, he came to the hospital.

Examination. Positive Findings.—Exophthalmos of the left eye, of the non-pulsating type; no bruit on auscultation over the head; complete blindness of the left eye; impaired vision, with a tendency toward hemianopsia for colors, in the right eye; optic atrophy in the left eye; well marked choked disc in the right; weakness of all the extraocular muscles of the left side; motor and sensory disturbances of the left trigeminal nerve.

Operative Treatment.—A correct diagnosis of aneurism was not made, and with the supposed growth well located by the X-ray plate, an attempt at radical extirpation was suggested. This the patient refused. A simple subtemporal decompression was therefore done upon the right side for the relief of pressure symptoms. The relief was complete and the choked disc in the right eye completely subsided. The patient returned to work and remained at work for a period of 18 months. He was then again seized with a sudden terrific headache, became unconscious, was brought to the hospital as soon as possible, but died an hour after his admission.

Autopsy.—A view of the base of the brain (Fig. 5a) shows a large aneurism occupying the left temporal fossa and extending beyond the median line to the right. It was, at the time of removal of the brain, entirely covered by the dura and fixed to the bone at the carotid canal. Upon the right side is a second smaller aneurism, 3.5 x 2 x 2 cm. in diameter, which has eroded the floor of the sella turcica. The hypophysis lies between the two masses, much compressed and flattened. The large mass on being separated from the brain shows clearly the internal carotid artery entering and leaving it at almost opposite poles. The vessels are of about normal size. The mass measures 24 cm. in circumference and 8 x 7 x 7 cm. in its various diameters. Its surface is smooth and roughly spherical, with the exception of three projecting knobs. On section, the wall of the aneurism varies from 1 cm. in thickness to paper thinness, and shows numerous areas of calcification. The sac is entirely filled with a laminated clot which can be lifted out *en masse*; the aneurism therefore being entirely solid except for a narrow channel extending through the clot. The base of the brain, after removal of the mass, shows an almost complete destruction of the tip of the left temporal lobe. The midbrain is compressed and dislocated to the right. The optic chiasm is rotated through an angle of 90 degrees, so that it lies flattened against the mesial aspect of the frontal lobe. On section of the brain the right ventricle is dilated; the left, collapsed. The tip of the left temporal lobe has undergone an extensive cystic degeneration.

Examination of the skull after removal of the brain shows complete destruction of the posterior wall of the left orbit, destruction of the left anterior and both posterior clinoid processes, partial destruction of the right anterior clinoid process, and erosion of the floor of the sella turcica.

Comments.—One of the most interesting features of this case is the X-ray picture. As previously noted, the calcified areas are in the form of more or less concentric, thin lamellae. In retrospect, we should have suspected aneurism, for, in reviewing the cases in the literature and our own cases of calcified tumor, we have found no instance in which the calcification of a true tumor has been of this nature.

4. Surgical No. 34653. Fig. 6. The roentgenogram shows a small spherical area .8 cm. in diameter situated immediately above and anterior to the posterior clinoid processes. So close is it situated to these processes that it might readily be mistaken for their continuation. Stereoscopic examination, however, demonstrates its independence. The sella turcica is perhaps slightly enlarged. The case, verified by autopsy, is one of cyst arising from Rathke's pouch, the shadow in the roentgenogram representing an area of calcification in its wall. It illustrates the point that a shadow in the roentgenogram may give no idea of the size of the lesion.

Clinical Note.—A white, married female, aged 20, was admitted to the hospital May 25, 1914, complaining of blindness. The present illness began two years previously with severe nocturnal headaches. These were periodic, gradually increasing in intensity; occasionally accompanied by vomiting. Soon after the onset of the illness dimness of vision was noticed. This alternated with periods of normal vision until two months before admission. Since that time vision has rapidly declined, and on admission she was totally blind.

Examination. Positive Findings.—Blindness in both eyes; primary optic atrophy; the typical glandular picture of Fröhlich's dystrophia adiposogenitalis.

Operative Treatment.—A diagnosis of suprasellar lesion was made. By an intracranial hypophyseal approach a large cyst was exposed lying directly behind the optic chiasm. This cyst was evacuated. The patient recovered from the operation. Vision returned to a remarkable extent. The visual field in the right eye returned almost to normal; in the left eye there remained a temporal hemianopsia. The patient remained well for a year, and then returned with symptoms identical with those at her first admission. A second operation was performed. An attempt to remove the cyst wall was made. The patient succumbed.

Comments.—The X-ray in this case was of the greatest help in arriving at a diagnosis of a suprasellar lesion. The autopsy established the presence of a calcified area in the cyst wall quite independent of the posterior clinoid processes.

5. Surgical No. 39145. Fig. 7. The shadow in this case is almost identical with the preceding. It represents apparently a more or less spherical bony knob approximately .9 x .5 cm. in diameter lying upon the posterior clinoid processes. The sella turcica is more flattened than in the preceding case and the distance between the anterior and posterior clinoids greater. This case, verified at operation, is one of tumor of the optic nerve sheath.

Clinical Note.—A girl 21 years of age was admitted February 6, 1915, complaining of loss of vision. Her visual disturbance dates back seven or eight years, beginning with a blurring of objects, progressing to a hemianopsia, and finally to total blindness in the left eye; to a hemianopsia with marked impairment of vision in the right eye. She has had periodic headaches since the onset of her illness, never severe and not associated with nausea or vomiting.

Examination. Positive Findings.—A slender, normal-appearing girl; no acromegalic features; no signs of hypopituitarism; primary optic atrophy of both discs; complete blindness in the left eye; a temporal hemianopsia for form and colors in the right eye.

Operative Treatment.—An intracranial approach upon the left side exposed the chiasmal region satisfactorily. There presented between the optic nerves a hard, spherical tumor about 1.5 cm. in diameter, attached by a pedunculated base to the left optic nerve. After its attachment to the nerve had been cut across it was appa-

rent that the tumor arose from the nerve sheath and that tumor-tissue extended into the left optic nerve. Further exposure showed that the right optic nerve and the chiasm were involved. The bony portion of the tumor shown in the X-ray was freely movable.

The patient is living. Her vision has remained stationary.

6. Surgical No. 33012. Fig. 8. The interest in the roentgenogram relates to the sella turcica. It is definitely outlined, measures 1.6 cm. in its antero-posterior diameter, and is about 1.4 cm. deep. The distance between anterior and posterior clinoids is increased. Within the sella turcica is a dense shadow, due apparently to the calcification of the entire hypophysis. Owing to this shadow it is difficult to make accurate statements regarding the anterior and posterior clinoid processes. The anterior clinoids are apparently intact; the posterior clinoids appear to have been destroyed. There is no destruction of the floor of the sella turcica. The sphenoidal sinus is unusually large, its greatest antero-posterior diameter being 4.5 cm., its greatest width 1.5 cm.

Clinical Note.—A white, married male, aged 44 years, entered the hospital October 9, 1914, complaining of loss of vision. The present illness began one year before admission with dimness of vision in the right eye and some disturbance of hearing in the right ear. He became totally blind in his right eye in March, 1914, and had marked impairment of vision in his left eye. In the past three or four months he has had attacks of vertigo and staggering; for three months has suffered from headache confined to the right occipital region; and for four months has had subjective numbness of the right side of the face.

Examination. Positive Findings.—A large, well-nourished man, totally blind in both eyes; a double choked disc of 4 diopters, with scattered hemorrhages upon the discs and retina; nystagmoid movements to the right; hyperesthesia to pain, touch, and temperature on the right side of the face; slight right facial weakness; complete deafness to air conduction in the right ear.

Operative Treatment.—The diagnosis was indefinite. Because of his total blindness we were unable to test his visual fields, and hesitated to make a diagnosis of a lesion about the chiasm. The clinical signs suggested a cerebellopontine lesion, and a cerebellar exploration was undertaken. The lesion was not found, either in the cerebellar hemisphere or in the cerebellopontine angles. The patient was discharged relieved of his headaches and with a subsidence of his choked discs.

Comments.—The lesion is not certified. In retrospect we are inclined to believe, in view of the positive shadow in the sella turcica, that the lesion is an hypophyseal one.

In this small number of cases (6 per cent) the X-ray establishes not only the diagnosis but also the location of the tumor. In the two cases of suprasellar lesion, the diagnosis, to one not familiar with the variations in the conformation of the posterior clinoid processes, would have been difficult perhaps from the X-ray alone. Indeed, one of these cases was sent to us with X-rays taken elsewhere which were reported to be normal. Yet in a careful examination of over 200 roentgenograms (tumor, epilepsy, etc.) we have in no instance seen a normal variation in the posterior clinoid processes which could be confused with the condition seen in these cases.

The roentgenogram which shows incomplete ring-shadows is of particular interest. The shadow as a whole differs so markedly from that in solid tumors that we should have been

able to make a differential diagnosis between a solid and a hollow lesion; and it is possible that in subsequent cases such a differential diagnosis may be made.

Shadows Due to Calcification of the Choroid Plexus, Pineal Gland and Meninges (Table III).—The discussion of roentgenographic shadows due to the calcification of brain tumors

TABLE III. SHADOWS DUE TO THE CALCIFICATION OF THE MENINGES, PINEAL GLAND AND CHOROID PLEXUS.

X-Ray No.	Structure casting shadow.	Lesion causing symptoms.	Location of lesion.	Verified at
23011	Choroid plexus.	Gumma of the dura mater.	Temporal region.	Operation.
3029				
34451	Falx cerebri.	Presumed tumor.	Unlocalizable	No.
34610				
21315	Pineal gland.	Glioma.	Central, subcortical.	Operation.
20557	"	Cyst.	Paracentral.	Operation.
18706	"	Glioma.	Temporal lobe.	Operation.
21760	"	Pachymeningitis interna hemorrhagica.	Hemisphere.	Operation.
19549	"	Glioma.	Hemisphere.	Operation.
24376	"			
29058	"	Endothelioma.	Paracentral.	Operation.
29878	"	Glioma.	Optic thalamus.	Autopsy.
30039	"			
35908	"	Glioma.	Parietal lobe, subcortical.	Autopsy.
15966	"	Adenoma.	Hypophysis.	Operation.
21639	"	Glioma.	Suprasellar.	Operation.
30810	"	Adenoma.	Hypophysis.	Operation.
35312	"	Adenoma.	Hypophysis.	Operation.
23090	"	Arachnoiditis.	Over cerebellum.	Operation.
32428	"	Aneurism.	Basilar artery.	Autopsy.
25217	"	Presumed cerebrale.	Unlocalizable	No.
35144	"	Tumor, metastatic.	Cerebellum.	No.
15280	"	Tumor.	Cerebellum.	No.
17842	"	Tumor.	Presumed cerebellar.	No.

should not be dismissed without mention of shadows the result of calcification of structures normally present in the intracranial space; for, unless the character and usual position of such shadows are known, they might well be confused with tumor-shadows. In the roentgenograms of patients presenting clinical evidences of tumor we have observed shadows due to the calcification of the choroid plexus, pineal gland and falx cerebri.

Choroid Plexus (Fig. 9).—In the single case which we have had, the shadow is lobate, lying about 3 cm. above and slightly posterior to the petrous portion of the temporal bone. Seen in the single plate, the shadows of the two choroid plexuses are superimposed. With stereoscopic vision, two symmetrically placed shadows occupy corresponding positions in the two hemispheres. In an antero-posterior roentgenogram the shadows are projected to the upper inner angle of either orbit. The patient whose roentgenogram shows this shadow is living after the removal of a dural gumma. The shadow, therefore, has not been certified.* A similar shadow

* Since the preparation of this paper a second case of calcification of the choroid plexus has come under observation. The autopsy showed extensive calcification of the choroid plexus; and by post-mortem studies the shadow in the roentgenogram has been identified with this structure.

has been described by Schüller, who also interprets it as due to calcification of the choroid plexus.

Pineal Gland (Fig. 10).—The pineal gland seems especially prone to calcification. In the roentgenograms of 17 patients its shadow is round or oval, varying from small size to 4 or 5 mm. in diameter, and situated in the midline from 1.5 to 2.5 cm. directly above the temporal bone. We have identified this shadow with the pineal gland by autopsy studies. Although in our experience it has had no pathological or diagnostic significance, variations in its size or position might be of value in the diagnosis of tumors of or about the pineal gland.

Falx Cerebri (Figs. 11 and 11a).—A shadow due to an area of calcification in the falx cerebri is present in the roentgenogram of one patient. A single plate (lateral view) shows a definite shadow, crossed apparently on either side by the greatly dilated meningeal arteries, suggesting a calcified tumor in the precentral region. The stereoscope, however, and more certainly an antero-posterior roentgenogram, show it to be exactly in the midline; and, although not certified, it is in all probability due to an area of calcification in the falx cerebri.

Shadows due to the calcification of structures other than those mentioned undoubtedly occur. Attention has been called to calcification in the walls of the cerebral vessels, in Pachionian granulations, in the meninges associated with epilepsy or following old hemorrhages. Our experience is too limited to warrant comment upon them.

Pseudo-shadows.—The term is applied to various light and dark areas in roentgenograms of the skull, which may be confused with true tumor-shadows. In our study we have often seen so-called pseudo-shadows. They occur most frequently in the temporal fossa and in the occipital, suboccipital and frontal regions. In our experience they have no significance. They can be readily distinguished from the shadow of a calcified tumor, and can scarcely be confused with circumscribed areas of diminished density, the result of atrophic changes in the skull over cerebral growths.

II. CHANGES IN THE SKULL DUE TO BRAIN TUMOR.

Our study early showed us that uncalcified brain tumors fail to cast shadows in the roentgenogram, and that calcified or bony tumors are rare (6 per cent). A study of the roentgenographic changes in the skulls of patients with brain tumor was therefore begun in the hope of deriving information of diagnostic value. Attempting to correlate the clinical and roentgenographic manifestations of brain tumor, we have grouped these changes into those due to *general pressure*—the result of a tumor anywhere within the intracranial space—and those due to *local pressure*—the result of a tumor within or in immediate proximity to the part affected.

(A) CHANGES IN THE SKULL DUE TO GENERAL PRESSURE.

(FIGS. 12 AND 13.)

Those which can be recognized in the roentgenogram are: (1) Enlargement of the skull; (2) separation of the cranial sutures; (3) general convolitional atrophy; and (4) destruction of the sella turcica or atrophy of its posterior clinoid

processes. The atrophy of the skull in the temporal region so often seen at operation cannot with certainty be recognized in the roentgenogram. The vascular changes in the skull, frequently a manifestation of general pressure, are considered under a special heading. Produced by the pressure of the brain against the inner table of the skull, these general pressure changes may be due either to cerebral or posterior fossa tumors. It should be remembered, however, that the mechanism of the production of increased intracranial tension in *cerebral* differs from that in *posterior fossa* tumors. In the former the increased pressure is commonly the result of an increase in the intracranial contents due to the growth of the lesion; in the latter it is caused, not so much by the lesion itself, as by the occlusion by it of the iter and the consequent production of an internal hydrocephalus. Clinically, it is recognized that increased intracranial pressure develops more rapidly and reaches a higher grade in posterior fossa than in cerebral tumors; a fact which is substantiated by our roentgenographic studies.

Undoubtedly age plays an important rôle in these general pressure signs. Obviously, separation of the sutures with consequent enlargement of the skull and atrophy of the inner table take place more readily in the young.

(1) *Enlargement of the Skull* (Table IV (1), Fig. 12).—The roentgenograms of nine patients show a definite enlargement of the skull. The oldest patient is 18 years of age. The condition is associated in every instance with separation of the cranial sutures and, in most, with thinning and general convo-

TABLE IV. GENERAL PRESSURE SIGNS OF INTRACRANIAL TUMORS AS SEEN IN THE X-RAY PLATE.

1. ENLARGEMENT OF THE SKULL.*

X-Ray No.	Character of enlargement.	Location of lesion.	Verified at
1 29000	General enlargement.	Suprasellar (glioma).	Operation and autopsy.
2 15311	"	"	"
3 5824	"	"	"
3 15409	"	" frontal—	"
4 26471	"	"	"
5 34779	"	"	"
3 5472	"	"	"
6 34287	"	"	"
7 34713	"	"	"
8 33425	"	"	"
9 34253	"	"	"
5 39531	"	"	"

* X-Ray Nos. 25954 and 35739, not included in this series, are examples of enlargement of the head, separation of the cranial sutures, and convolitional atrophy occurring in cases of certified cerebral abscess without an internal hydrocephalus.

lutional atrophy of the skull. These three phenomena of general pressure are therefore commonly associated. Of the nine patients, eight had cerebellar or cerebellopontine lesions associated with an internal hydrocephalus, and one had a suprasellar lesion with an obstructive hydrocephalus due to the occlusion of the third ventricle. Although, then, enlargement of the skull is most commonly seen in association with subtentorial lesions, it may occur in association with cerebral tumors causing an obstructive hydrocephalus. It may occur, though rarely, in cerebral lesions without an associated internal hydrocephalus,

as two cases of cerebral abscess, not included in this series, have shown.

(2) *Separation of the Cranial Sutures* (Table IV (2), Figs. 12 and 13).—Owing to the great variation in the prominence of the suture lines in apparently normal skulls, it has been difficult to differentiate between the slight grades of dias-

TABLE IV. GENERAL PRESSURE SIGNS OF INTRACRANIAL TUMORS AS SEEN IN THE X-RAY PLATE.—Continued.

2. SEPARATION OF THE CRANIAL SUTURES.*

X-Ray No.	Sutures involved.	Degree.	Location of lesion.	Verified at
1 18706	F. P.	Slight	Temporal lobe (glioma).	Operation.
2 21760	O. P.	Marked	Hemisphere (pachym. int. hemorrhagic).	Operation.
3 1457	F. P. and O. P.	Slight	Temporal lobe (glioma).	Operation.
24376				
4 25752	F. P. and O. P.	"	Temporal lobe (glioma).	Operation.
5 23610	F. P. and O. P.	"	Hemisphere (subcort. glioma).	Autopsy.
6 25610	F. P. and O. P.	"	Frontal lobe (endothelioma).	Operation.
7 23893	F. P.	"	Paracentral (glioma?).	Operation.
8 23717	F. P.	"	Temporal lobe (cyst).	Operation.
9 29058	O. P.	"	Paracentral (endothelioma).	Operation.
10 29058	O. P.	"	Hemisphere (subcort. glioma).	Autopsy.
11 27982	F. P. and O. P.	"	Temporal (dural gumma).	Operation.
12 27975	F. P.	"	Hemisphere (subcort. glioma).	Operation.
13 29878	F. P. and O. P.	"	Hemisphere (subcort. glioma).	Autopsy.
30872				
14 29329	O. P.	"	Frontal lobe (endothelioma).	Operation.
15 31938	O. P.	"	Hemisphere (bilateral endothelioma).	Operation; autopsy.
31987				
16 35908	F. P. and O. P.	"	Parietal lobe (subcort. glioma).	No.
17 19504	F. P. and O. P.	"	Hypophysis.	No.
18 23254	F. P. and O. P.	Marked	Hypophyseal and suprasellar (cyst).	Operation; autopsy.
26485				
19 29000	F. P. and O. P.	"	(all sutures involved) Suprasellar (glioma).	Autopsy.
20 30810	O. P.	Slight	Hypophysis (adenoma).	Operation.
21 55312	O. P.	"	Hypophysis (adenoma).	Operation.
22 35387	F. P. and O. P.	"	Suprasellar (sarcoma optic nerve).	Operation.
23 16386	F. P.	"	Cerebellum (glioma).	Autopsy.
24 15134	F. P. and O. P.	Marked	Cerebellum (cyst).	Operation.
25 15111	F. P. and O. P.	"	Cerebellum (cyst).	Operation.
35424				
26 17276	F. P. and O. P.	"	Cerebellopontine (endothelioma).	Operation.
27 15409	F. P. and O. P.	"	Cerebellum (glioma).	Operation.
28 25637	F. P. and O. P.	Slight	Cerebellum (cyst).	Operation.
29 27041	F. P. and O. P.	"	Cerebellum (cyst).	Operation.
30 26471	F. P. and O. P.	Marked	Cerebellum (cystic glioma).	Operation.
31 34779	F. P. and O. P.	"	Cerebellum (cyst).	Operation.
32 33072	F. P. and O. P.	Slight	Cerebellopontine (endothelioma).	Operation.
33 34287	F. P. and O. P.	Marked	Cerebellum (glioma).	Operation.
34 34713	F. P. and O. P.	Slight	Cerebellopontine (endothelioma).	Operation.
35 34287	F. P. and O. P.	"	Pons (aneurism, basilar).	Autopsy.
36 29696	F. P. and O. P.	Fairly	Pons (glioma).	Autopsy.
37 33425	F. P. and O. P.	Marked	Pons (glioma).	Autopsy.
38 35031	F. P. and O. P.	Marked	Cerebellum (cyst).	Operation.
39 17519	F. P. and O. P.	Slight	Presumed cerebral (metastatic).	No.
40 17426	F. P. and O. P.	"	"	No.
41 20112	F. P. and O. P.	Marked	Presumed cerebral.	No.
42 20717	O. P.	Slight	"	No.
43 21035	F. P.	"	"	No.
44 19314	F. P. and O. P.	"	"	No.
45 20650	F. P. and O. P.	"	"	No.
46 16590	F. P. and O. P.	"	"	No.
47 28790	F. P. and O. P.	"	"	No.
48 27017	F. P. and O. P.	"	"	No.
49 28733	F. P. and O. P.	"	"	No.
50 28872	F. P. and O. P.	"	"	No.
51 30777	F. P. and O. P.	"	"	No.
52 30395	F. P. and O. P.	"	"	No.
53 35489	F. P. and O. P.	"	"	No.
54 23907	F. P. and O. P.	Marked	Presumed cerebellar.	No.
55 21728	F. P. and O. P.	"	"	No.
56 15478	F. P. and O. P.	Slight	"	No.
57 15635	F. P. and O. P.	"	"	No.

* X-Ray Nos. 35739 and 25754, cases of certified cerebral abscess not included in this series, show marked separation of the sutures.

The fronto-parietal (coronal) and the occipito-parietal (lambdoid) sutures were particularly examined and our observations are confined largely to them.

tasis and normal variations. Attempting to be fair in our interpretation, separation of the sutures occurs in the roentgenograms of 57 patients. In those of 41 patients the diastasis is of such mild grade as to have little significance. Nineteen of these patients had cerebral tumors, 14 presumed cerebral tumors, 5 cerebellar, 2 presumed cerebellar tumors and 1 a tumor of the pons. In those of 16 patients the separation of

the sutures is marked. Eight of these patients had cerebellar tumors, 2 presumed cerebellar tumors, 2 pontine tumors, 2 suprasellar tumors associated with internal hydrocephalus, 1 a cerebral and 1 a presumed cerebral tumor. It is evident from this analysis that well-marked separation of the sutures is an infrequent finding in roentgenograms of patients with cerebral tumor, but a common finding in patients with cerebellar or posterior fossa tumors.

(3) *General Convolutional Atrophy* (Table IV (3), Figs. 12 and 14).—The term is used in the sense of Spiller to describe a form of pressure atrophy of the inner table of the skull most characteristically seen in the roentgenograms of patients with "idiopathic" internal hydrocephalus. As seen

TABLE IV. GENERAL PRESSURE SIGNS OF INTRACRANIAL TUMORS AS SEEN IN THE X-RAY PLATE.—Continued.

3. GENERAL CONVOLUTIONAL ATROPHY.*

N. Ray No.	Degree of atrophy.	Location of lesion.	Verified at
12725	Slight.....	Hemisphere (subcortical atrophy, glioma).	"
2599-1	"	Optic thalamus (glioma).....	"
19807	"	"	"
31445	Slight, more marked frontal	Temporal fossa (aneurism).....	"
427173	"	Hemisphere (arach. cyst).....	"
52121-2	Well marked.....	Suprasellar (glioma).....	Operation.
26235	"	"	"
26013	"	"	"
62000	Marked.....	Suprasellar (glioma).....	Autopsy.
73531-2	Slight.....	Hypophysis (adenoma).....	Operation; autopsy.
82122-2	Marked.....	Cerebellum (glioma).....	Operation.
91638	Slight.....	" (glioma).....	Autopsy.
107534	Marked.....	" (cyst).....	Operation.
1115511	"	" (cyst).....	"
13098	"	"	"
125406	"	" (glioma).....	"
130906	Slight.....	" (arachnoiditis).....	"
1127-41	"	" (cyst).....	"
133472	Marked.....	" (cyst).....	"
35472	"	"	"
163242	Slight.....	Pons (aneurism, basil. art.).....	Autopsy.
173043	Well marked.....	" (glioma).....	"
826343	Marked.....	Cerebellum (cyst).....	Operation.
1-3525	Slight.....	Cerebellopontine (endotheloma).....	Operation; autopsy.
2917426	"	Presumed cerebral (meta-No. stasis).....	"
212105	"	Presumed cerebral.....	"
2215234	"	"	"
2221204	"	"	"
2221204	"	"	"
222967	Marked.....	Presumed cerebellar.....	"
25334-9	Slight.....	" cerebellar.....	"
262172	Marked.....	" cerebellar.....	"
2715635	Slight.....	" cerebellar.....	"

* N. Ray Nos. 3573 and 25754, cases of certified cerebral abscess not included in this series, show slight convolutional atrophy.

in the roentgenograms of patients with brain tumor, it may be local or general. Since a cerebral tumor exerts its greatest pressure locally, at least in the early stages of its growth, it may cause a local convolutional atrophy of the skull—a condition which will subsequently be spoken of. General convolutional atrophy of the skull may be seen in the late stages of cerebral tumors or as the result of internal hydrocephalus due to posterior fossa lesions.

The roentgenograms of 21 patients show a general convolutional atrophy of the skull. In those of 16 patients it is slight or merely suggestive and, except as an indication of general pressure, has little value in diagnosis. Four of these patients had cerebral, 6 presumed cerebral, 5 cerebellar and 1 presumed cerebellar tumors. In those of 11 patients general convolutional atrophy is marked. Six of these patients had cerebellar, 2 presumed cerebellar, 1 pontine and 2 supra-

sellar tumors with an associated internal hydrocephalus. These findings again are suggestive, indicating that marked general convolutional atrophy is more commonly seen in sub-tentorial or in suprasellar tumors which have caused an internal hydrocephalus.

(4) *Destruction of the Sella Turcica or Atrophy of Its Posterior Clinoid Processes* (Table IV (4), Figs. 12 and 13).—A proper interpretation of roentgenograms of the skull is of particular importance in considering deformations of the sella

TABLE IV. GENERAL PRESSURE SIGNS OF INTRACRANIAL TUMORS AS SEEN IN THE X-RAY PLATE.—Continued.

4. DESTRUCTION OF THE SELLA TURCICA OR ATROPHY OF THE POSTERIOR CLINOID PROCESSES.

N. Ray No.	Condition of sella.	Location or lesion.	Verified at
134779	Complete destruction.....	Cerebellum (cyst).....	Operation.
35472	"	" (glioma).....	"
234287	"	" (glioma).....	"
335621	" (practically).....	" (glioma).....	"
421760	Marked destruction.....	Hemisphere (pachym. int. hemorrhagic).....	"
520557	Atrophy posterior clinoid processes	Paracentral (cystic glioma).....	"
615451	"	Hemisphere (subcort. gli. Autopsy. oma).....	"
725732	"	Temporal lobe (glioma).....	Operation; autopsy.
855610	"	Frontal lobe (endotheloma).....	Operation.
927239	"	Hemisphere (subcort. gli. Autopsy. oma).....	"
1016388	"	Cerebellum (glioma).....	Autopsy.
1113311	Marked destruction.....	" (cyst).....	Operation.
33854	"	"	"
1231259	Atrophy posterior clinoid processes	Cerebellopontine (endotheloma).....	"
1320112	Complete destruction.....	Presumed cerebral.....	No.
1421304	Atrophy posterior clinoid processes	"	"
1523007	Marked destruction.....	" cerebellar.....	"
1630777	Atrophy posterior clinoid processes	" cerebellar.....	"
1730355	"	"	"
181345	"	" cerebellar.....	"
1916456	Complete destruction.....	Temporal fossa (aneurism).....	Autopsy.
2018706	Atrophy posterior clinoid processes	lobe (glioma).....	Operation.
2132555	Flattening post. clinoid processes.	Presumed cerebral.....	No.

turcica; for we are rather prone to consider destruction of the sella turcica as indicative of hypophyseal or suprasellar lesions. Aside from these conditions, destruction of the sella turcica or atrophy of its posterior clinoid processes may take place as a result of the local pressure of cerebral tumors arising in the immediate neighborhood of the sella, or because of general increased intracranial pressure due to cerebral or sub-tentorial lesions. The roentgenograms of 21 patients, none of whom had hypophyseal or suprasellar tumors, show destruction of the sella turcica or atrophy of its posterior clinoid processes. In those of 8 patients, 4 of whom had cerebellar, 1 presumed cerebellar, 2 cerebral and 1 presumed cerebral tumors, there is a marked or complete destruction of the sella turcica. From the position of the lesions, the sellar destruction must be considered a general pressure phenomenon, in the patients with cerebellar tumor, possibly due to the distention of the third ventricle. In the patients with aneurism of the internal carotid artery the sellar destruction is probably due to local rather than general pressure. In the roentgenograms of 13 patients, slight changes in the sella turcica, i. e., atrophy or disappearance of the posterior clinoid processes, is evident; 6 had cerebral, 4 presumed cerebral, 2 cerebellar and 1 presumed cerebellar tumors. It is perhaps noteworthy that these slight sellar changes are not associated with separation of the sutures

and general convolucional atrophy. In the patients with cerebellar, or with cerebral tumors lying at some distance from the sella turcica, atrophy of the posterior clinoid processes must be regarded as due to general pressure. In four patients the tumor lay in the subcortical tissues of the hemisphere immediately adjacent to the sella, and in them atrophy of the posterior clinoid processes may be considered a local pressure phenomenon.

To briefly summarize the changes in the skull due to general increased intracranial pressure, we may say that enlargement of the skull is not infrequently seen in the young and generally in association with an internal hydrocephalus due to a posterior fossa lesion. Separation of the sutures, general convolucional atrophy and destruction of the sella turcica are seen rarely and to but a slight degree in cerebral lesions; they are seen commonly and to a marked degree in cerebellar or posterior fossa lesions. Slight grades of these changes thus far in our own experience have had no focal diagnostic significance; marked grades, when occurring as they usually do in combination in the same case, indicate a subtentorial lesion which has caused an internal hydrocephalus. They may indicate a suprasellar lesion associated with an obstructive hydrocephalus.

It is especially in the differential diagnosis between cerebral and subtentorial tumor that the presence in the roentgenogram of general pressure signs is helpful. Yet they proved of no aid in the cases of two patients, blind on admission to the hospital, in whom the differential diagnosis lay between hypophyseal or suprasellar and cerebellar tumor. The histories suggested a cerebellar tumor; the clinical signs, total destruction of the sella turcica, optic atrophy and the syndrome of hypopituitarism, pointed to an hypophyseal or suprasellar growth. We explored the cerebellum of one patient in whom at autopsy we found a large suprasellar tumor; in the other, we found at operation a cerebellar cyst. Needless to say our inability to examine their visual fields was largely responsible for the difficulties in making a differential diagnosis.

(B) LOCAL CHANGES IN THE SKULL DUE TO BRAIN TUMOR.

The local effects of brain tumor upon the skull are commonly destructive, as seen in the local atrophy of the vault over a tumor or the destruction of the sella turcica; yet a local hypertrophy of the skull over a tumor may occur and, instead of destruction, the sella turcica may, at least in the early stages of disease, show an enlargement or hypertrophy as seen in acromegaly. The local changes in the skull which we have observed are: (1) Local hypertrophic changes in the skull; (2) local enlargement without destruction; (3) local atrophic changes in the skull; (4) local convolucional atrophy, and (5) local destruction of the sella turcica.

(1) *Local Hypertrophic Changes in the Skull* (Table V (1), Fig. 15).—The roentgenograms of five patients show a well-marked, circumscribed hypertrophy of the vault; in one responsible for a diagnosis of osteoma of the skull. In four patients operation showed that the hypertrophied bone lay

TABLE V. LOCAL CHANGES IN THE SKULL DUE TO INTRACRANIAL TUMORS.

1. LOCAL HYPERTROPHY OF THE SKULL OVER TUMORS.

X-Ray No.	Condition.	Location and character of lesion.	Verified at
1 17554	Local hypertrophy over tumor.	Hemisphere cerebral tubercle...	Operation.
2 10353	Marked hypertrophy over frontal region; suggests Paget's disease.	Hemisphere presumed cerebral...	No.
3 25610	Local hypertrophy over tumor.	Hemisphere dural endothelioma.	Operation.
4 31538	" " " " " "	" " " " " "	" "
5 35952	" " " " " "	" " " " " "	" "

directly over a superficial tumor; in one it failed to disclose the lesion. The condition apparently is rare, for in our study of the literature we have not seen it mentioned. The mechanism of its production is not clear. In three patients the lesion found at operation was a dural endothelioma; in one a superficial, solitary tubercle. In all, the dura lying between bone and tumor, while intact, showed a great increase in vascularity, as did the hypertrophied bone; and it seems possible that the local increase in the blood supply may explain the local hypertrophy of the skull.

(2) *Local Enlargement of Structures of the Skull* (Table V (2), Fig. 12).—Enlargement of the Internal Auditory Meatus: The herniation of the cerebellum into the foramen magnum and, occasionally, of the cortex into the foramina of exit of the cranial nerves, suggests that these structures may

TABLE V. LOCAL CHANGES IN THE SKULL DUE TO INTRACRANIAL TUMORS.—Continued.

2. LOCAL ENLARGEMENT OF STRUCTURES (WITHOUT DESTRUCTION).

X-Ray No.	Structure involved.	Location of lesion.	Verified at
134943	Sella enlarged (acromegaly).....	Hypophysis (adenoma).....	Operation.
2 18706	" enlarged wide.....	Temporal lobe (glioma).....	" "
3 33387	" widened anterior and posterior clinoids separated.	Chiasm and optic nerves (sarcoma).....	" "
4 23529	Sella enlarged and deepened.....	Suprasellar (cyst Rathke's pouch).....	Autopsy.
5 35144	" enlarged.....	Presumed cerebral.....	No.
5 35217	" " " " " "	" " " " " "	" "
6 15178	" " " " " "	Presumed cerebellar.....	" "
7 18087	" " " " " "	" " " " " "	" "
8 15594	" " " " " "	Hypophysis.....	" "
1 29000	Internal auditory meatus enlarged.	Suprasellar (glioma).....	Autopsy.
2 30810	" " " " " "	Hypophysis (adenoma).....	Operation.
3 32179	" " " " " "	Cerebellum (cyst).....	" "
4 15184	" " " " " "	" (cyst).....	" "
5 15311	" " " " " "	" (cyst).....	" "
35-24	" " " " " "	" " " " " "	" "
6 26471	" " " " " "	" (cystic glioma).....	" "
7 34287	" " " " " "	" " " " " "	" "
8 32428	" " " " " "	Pons (aneurism, basilar art.).....	Autopsy.
9 35931	" " " " " "	Cerebellum (glioma).....	Operation.
10 17519	" " " " " "	Presumed cerebral.....	No.
11 23907	" " " " " "	" cerebellar.....	" "

undergo enlargement recognizable in the roentgenogram. Thus far, however, we have been unable certainly to recognize such changes; and our remarks will be confined to the internal auditory meatus. Henschen²⁰ was the first to observe a unilateral enlargement of the internal auditory meatus due to the local erosion of a cerebellopontine tumor. At the autopsy he noted that the internal auditory meatus on the affected side was larger than on the opposite one, and expressed the view, which he was later able to substantiate, that the enlargement should be recognizable in the roentgenogram. We have studied

correct diagnosis. It is interesting to note that in the roentgenograms of four other patients with hypophyseal or suprasellar tumor there were slight changes of or about the sella turcica, but no sellar destruction—an indication of how mutually necessary to each other are clinical and roentgenographic signs in the diagnosis of these conditions. The importance of roentgenograms in determining the method of approach to these lesions will be discussed in a subsequent communication.

(C) VASCULAR CHANGES IN THE SKULL DUE TO BRAIN TUMOR.
(Table VI, Fig. 20).

Vascular abnormalities in the skull, the result of brain tumor, manifest themselves in the roentgenogram by an enlargement of the diploetic sinuses or an excessive grooving of the bone, either of vessels normally present or of newly formed and abnormally distributed vessels. Obviously, in-

TABLE VI. VASCULAR CHANGES IN THE SKULL DUE TO INTRACRANIAL TUMORS.

X-ray No.	Vascular changes.	Location of lesion.	Verified at
117554	Enlargement of meningeal A, bilateral	Precentral (tubercl.)	Operation.
219751	Enlargement of diploetic vein, frontal.	Paracental (subcort. gl.)	"
318706	Stellate diploetic veins, parietal region	Temporal lobe (glioma)	"
423026	Marked gen. dilatation esp. frontal.....	Frontal lobe (glioma)....	"
519340	" "	Hemisphere (subcort. gl.)..	"
24576	" "	" "	"
616456	Enlargement meningeal A, bilateral..	Temporal fossa (aneurism)	Autopsy.
725732	" " "	Temporal lobe (glioma) ..	Operation; autopsy.
925610	Enlarged vein from region of hyp. boue., unilateral.	Frontal lobe (endotheli-oma).	Operation.
923717	Enlargement meningeals and occipital	Temporal lobe (cyst arach.)	"
1026856	Enormous dilatation (unilateral) of	Occipital lobe (endotheli-	"
26891	meningeal.	oma).	"
1129058	General vascular enlargem't, bilateral.	Para central (endotheli-	"
1230238	Enlarged vein from region of tumor.....	Postcentral (osteosarcoma)	"
320263	" "	" "	"
1327165	Dilatation meningeals, slight bilateral.	Hemisphere (cyst arach.)..	"
237983	" " "	Temporal region (gumma).	"
1527975	General vascular enlargem't, bilateral	Precentral (glioma)	"
1629878	Enlargement meningeal A, bilateral..	Hemisphere (subcort. gl.).	Autopses.
30639	" "	" "	"
1729329	Dilatation meningeals slight, bilateral.	Frontal (endothelioma) ..	Operation.
1835765	" " "	Temporal lobe (glioma) ..	Operation; autopsy.
1935952	Enlarged vein from region of tumor,	Para central (endotheli-	Operation.
2015066	General vascular enlargement, slight.	Hypophysis (adenoma)....	"
2123254	Stellate diploetic veins, parietal region	(cyst).....	Operation; autopsy.
26435	" " "	" (cyst).....	Operation; autopsy.
2233436	" " "	" (adenoma).....	Operation; autopsy.
2335312	General vascular enlargement, slight..	" (adenoma).....	Operation; autopsy.
2425387	Enlargement meningeal A, slight.....	Suprasellar, sarc. chiasm.	Operation.
2521779	General enlargement, stellate diploet-	Cerebellum (cyst).....	"
ic veins.	" "	" "	"
2625057	Enlargement meningeal A, slight.....	Cerebellopontine (endothe-	"
2733072	" " " " " " " " " " " "	loma) over occiput.....	"
2832428	" " " " " " " " " " " "	Fons (aneurism, basil. art.)	Autopsy.
2931250	General vascular enlargement.....	Cerebellopontine (endothe-	Operation;
3017519	Enlargement meningeal A, bilat. slight	lioma),	autopsy.
3117305	" " " " " " " " " " " "	Presumed cerebral.....	No.
3220112	" " " " " " " " " " " "	" " " " " " " " " " " "	"
3320717	stellate diploetic veins	" " " " " " " " " " " "	"
3421035	" " " " " " " " " " " "	" " " " " " " " " " " "	"
3515214	" " " " " " " " " " " "	" " " " " " " " " " " "	"
3629850	" " " " " " " " " " " "	" " " " " " " " " " " "	"
3716590	" " " " " " " " " " " "	" " " " " " " " " " " "	"
3828790	General vascular enlargement.....	" " " " " " " " " " " "	"
3927017	Enlargement meningeal A, bilat. slight.	" " " " " " " " " " " "	"
4028733	" " " " " " " " " " " "	" " " " " " " " " " " "	"
4130777	General enlargement slight, stellate diploetic veins.	" " " " " " " " " " " "	"
4230365	General vascular enlargement, marked.	" " " " " " " " " " " "	"
434451	Enlargem't meningeal A, bilat. marked	" " " " " " " " " " " "	"
44510	" " " " " " " " " " " "	" " " " " " " " " " " "	"
4421728	General enlargement, stellate diploet-	" " Cerebellar.....	"
ic veins.	" "	" "	"
4515280	General enlargement, slight, bilateral.	" " " " " " " " " " " "	"
4615478	Enlargement vessels of frontal region	" " " " " " " " " " " "	"
4717842	Stellate diploetic veins, parietal.....	" " " " " " " " " " " "	"
4818037	Enlargem't meningeal A, bilat. marked	" " " " " " " " " " " "	"
4917077	" " " " " " " " " " " "	" " " " " " " " " " " "	"

creased intracranial pressure, regardless of the location of the lesion, may cause vascular stasis and a general enlargement of the cranial vessels demonstrable in the roentgenogram; a superficial tumor, a local increase in the number and size of the blood vessels of the adjacent dura and bone. In the roentgenograms of 50 patients we have noted an enlargement of the cerebral vessels, either a dilatation of the middle meningeal arteries or of the diploetic or extracranial sinuses of the skull. In those of 46 patients the dilatation is general and often of slight grade—an indication of increased intracranial pressure, but of no value in the focal diagnosis of brain tumor. It is seen most commonly in patients with cerebral or presumed cerebral lesions; more rarely in those with posterior fossa tumors. In the roentgenograms of four patients there is, as demonstrated with the stereoscope, a marked, in one, an enormous, *unilateral* dilatation of the cranial vessels—a finding of great value in the focal diagnosis of tumor. The roentgenograms clearly show a circumscribed network of vessels which drain into a single large vascular trunk. In all four patients the lesion at operation proved to be a dural endothelioma lying within the area outlined by the vascular network. In one, without other localizing signs, the unilateral vascular dilatation enabled us to make a positive focal diagnosis.

A stellate arrangement of the diploetic sinuses in the parietal region of the skull has been observed in the roentgenograms of eight patients. It occurs apparently regardless of the location of the lesion, and in our experience is merely a sign of venous stasis.

SUMMARY.

1. With the exception of the comparatively few which show definite tumor-shadows, roentgenograms of the head are merely an aid, though an important aid, in the diagnosis of brain tumor.
2. Uncalcified tumors do not cast shadows in the roentgenogram, unless tumor-tissue has invaded the accessory sinuses. A possible exception may be hypophyseal lesions which are viewed against the dark temporal fossa.
3. Calcified or bony tumors cast shadows which are readily recognized. In our experience such shadows occur in 6 per cent of patients with brain tumor. Judging from the literature, however, our experience has been fortunate.
4. The signs in the skull of increased intracranial tension, *i. e.*, enlargement of the skull, separation of the cranial sutures, general convolitional atrophy and destruction of the sella turcica, have a considerable value in the differentiation between cerebral and subtentorial lesions; for they indicate an internal hydrocephalus, which in our experience occurs only rarely in cerebral tumors, but is the usual accompaniment of posterior fossa tumors. It is of importance to remember that destruction of the sella turcica may be a general pressure phenomenon, especially in the differential diagnosis between suprasellar and cerebellar tumor in blind patients.
5. The local changes in the skull due to brain tumor are, in our experience, of greatest value in the diagnosis of hypo-

physcal or suprasellar lesions. The combination of characteristic eye-changes and local sellar destruction or enlargement makes the diagnosis the most certain, perhaps, of all intracranial conditions.

6. Local hypertrophy of the skull over cerebral tumors is of definite diagnostic value and has occurred in 4 per cent of our patients. Local atrophy of the skull over tumors is of equal diagnostic importance, but has occurred in only 2 per cent of the patients. Local unilateral vascular changes also have definite diagnostic significance and have occurred in 4 per cent of the patients. Local convolutional atrophy is of importance in the focal diagnosis of tumor only when demonstrably unilateral; in our experience this is rare. Local enlargement of the internal auditory meatus has thus far in our experience had very little diagnostic value.

7. The usual position and characteristic appearance of shadows due to the calcification of structures normally present in the intracranial chamber should be remembered.

8. In about 45 per cent of the patients in this series roentgenography has been of real diagnostic value.

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EXPLANATION OF PLATES.

Two pictures are shown over each figure number. The upper picture is the reproduction of a print made directly from the X-ray negative; the lower, a reproduction of a similar print retouched by an artist in order to emphasize abnormalities in the plate upon which we have commented in the text.

It should be remembered that the pictures represent positives of the X-ray negatives; and that, therefore, tumor-shadows, for example, which appear as dark shadows in the pictures appear as light areas in the X-ray plates.

CONTRIBUTION TO THE STUDY OF PROGNOSIS IN TUBERCULOSIS.¹

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The present study is taken from a larger and more exhaustive inquiry into various phases of tuberculosis which we have had in progress at Loomis Sanatorium for the past few years, and which, I hope, will be ready for publication within the year. In the course of this inquiry we have arrived at certain results which, when considered in connection with the statistical studies that have been made previously along similar lines—notably those of Brown and Pope² and Noel Bardswell³

—seem to justify some general conclusions as to prognosis, and in addition to suggest a more definite objective in treatment than has hitherto been emphasized.

I am not unmindful of the fallacy of drawing broad conclusions as to prognosis from the comparatively small numbers of cases so far dealt with. However, even though the numbers considered in any one of the available published reports be comparatively small, it does not follow that larger groups would show marked variation as to results, provided similar classifications were employed. Moreover, when approximately similar results are reached by different observers in the analyses of several relatively small groups, they would seem to have the weight of like results from a single analysis of a much larger group.

¹ Read before a meeting of the Laennec Society, May 5, 1916.

² Lawrason Brown and E. G. Pope: *The Ultimate Test of Sanatorium Treatment*. *Zeitschrift für Tuberkulose*, 1908, XII.

³ Noel Dean Bardswell: *Treatment of Pulmonary Tuberculosis*. *Lancet* (London), March 8 and March 15, 1913.

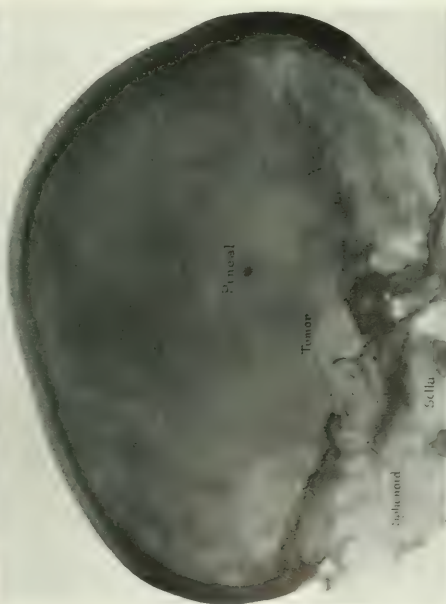
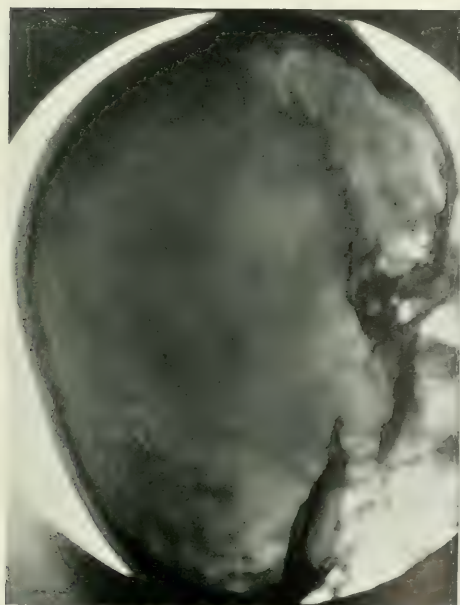


FIG. 1. Roentgenogram of a patient with a pituitary tumor. The floor of the sella turcica shows a defect through which the tumor has entered the sphenoidal sinus. The shadow cast by the tumor-tissue clouds the sinuses. The pineal gland casts a shadow.

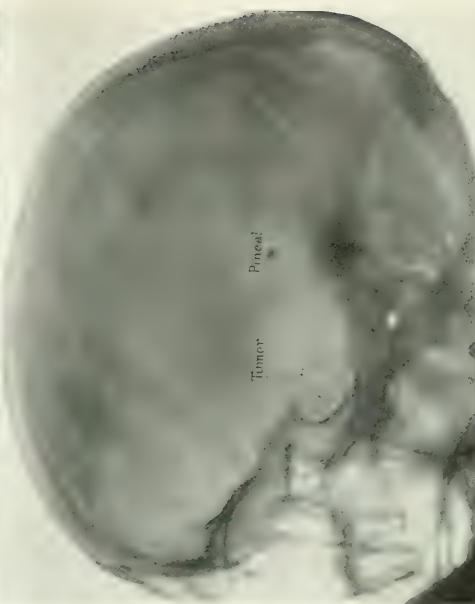
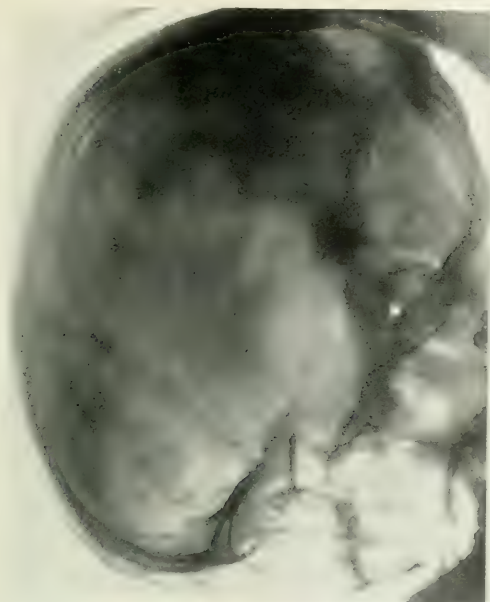


FIG. 2. Roentgenogram of a patient with a pituitary tumor. The sella turcica is enlarged, the posterior clinoid processes partially destroyed. Within the sella a definite shadow cast by the tumor is plainly visible.

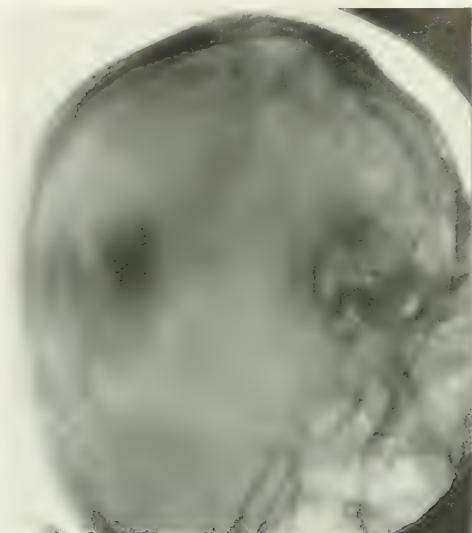


FIG. 4. Roentgenogram showing the shadow of an osteosarcoma of the skull. Seen with the stereoscope, the tumor extends well into the intracranial chamber.

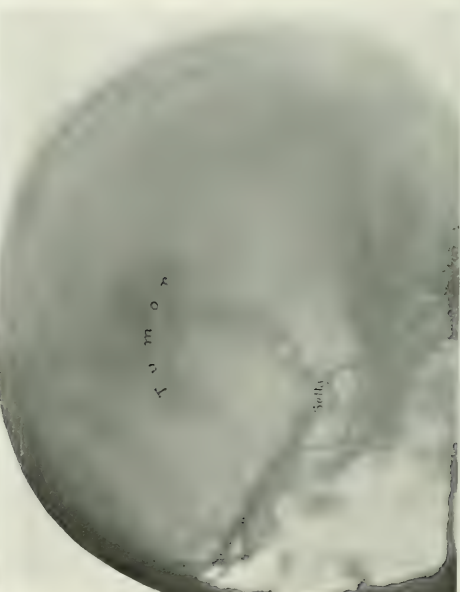


FIG. 3. Roentgenogram showing the shadow of a calcified tumor. The tumor is probably a suprasellar growth which has extended upward into the hemisphere.

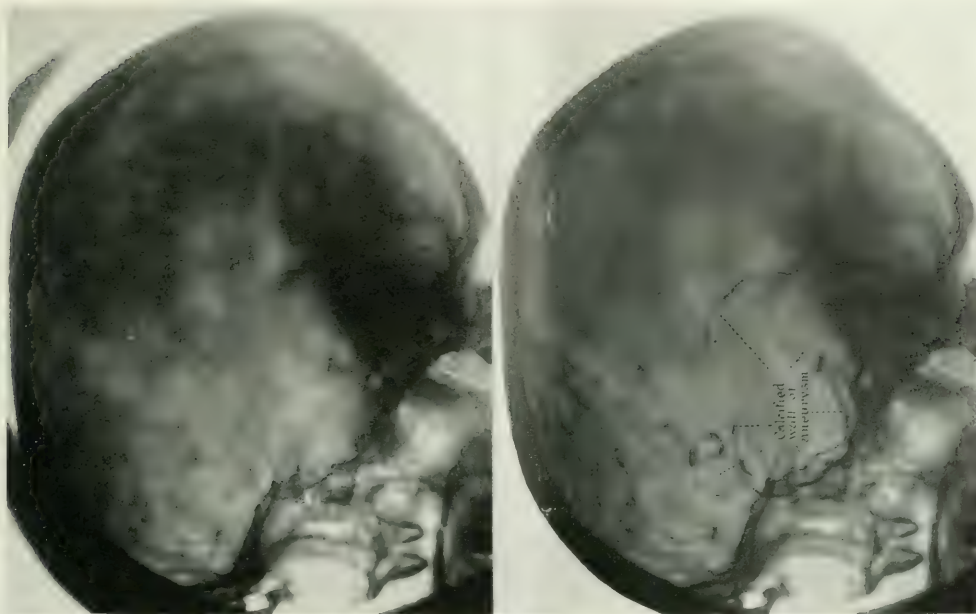


FIG. 5.—Roentgenogram showing the shadow cast by an aneurysm of the internal carotid artery. The areas of calcification in the wall of the sac appear as dark, heavy lines. The sella turcica appears to be completely destroyed. The local convulsional atrophy of the inner table is seen in the frontal region.

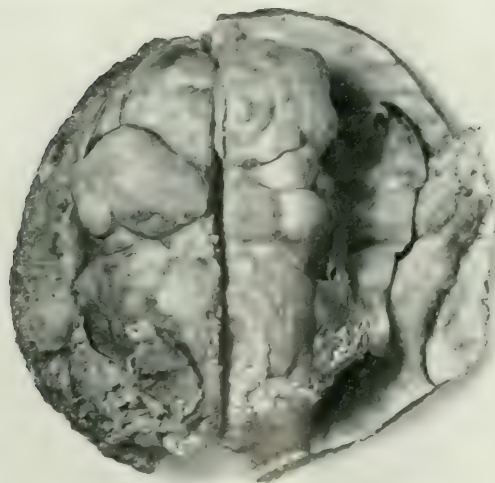


FIG. 4A. Specimen of osteosarcoma of the skull removed at operation. The bone and dura flaps were removed with the tumor. The roentgenographic shadow cast by this tumor is seen in Fig. 4.

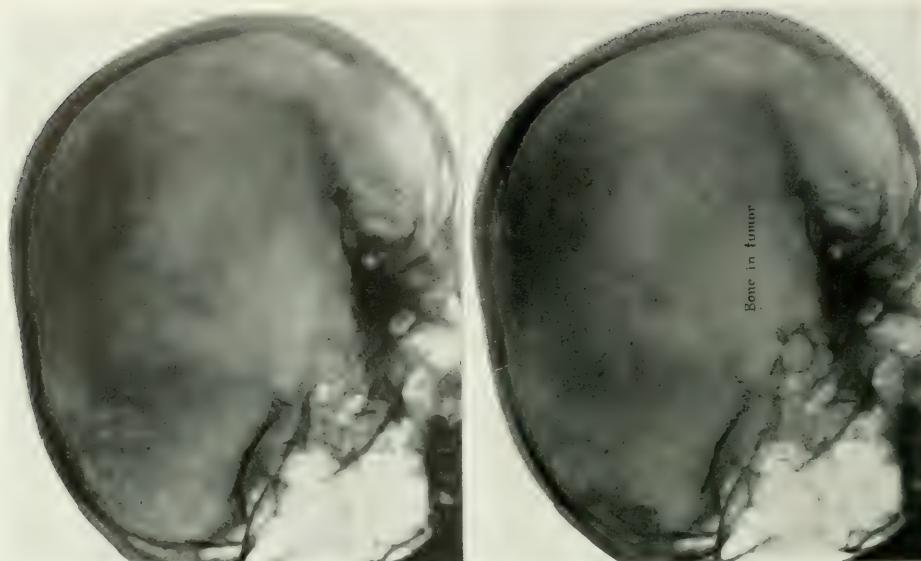


FIG. 6.—Roentgenogram of a patient with a suprasellar lesion (cyst of Rathke's pouch). The small shadow lying just above the posterior clinoid processes of the sella turcica is cast by an area of calcification in the wall of the cyst. Verified by autopsy studies.



FIG. 5A.—Specimen of aneurysm of the internal carotid artery. The roentgenographic shadow cast by this aneurysm is seen in Fig. 5.

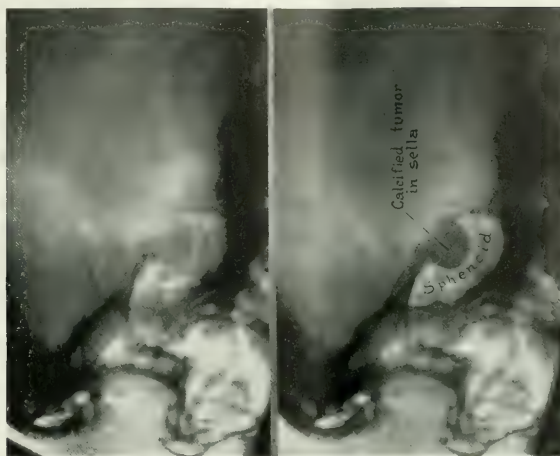


FIG. 8.—Roentgenogram showing the shadow cast by a calcified hypophyseal tumor. The shadow is so dense that the clinoid processes are obscured.

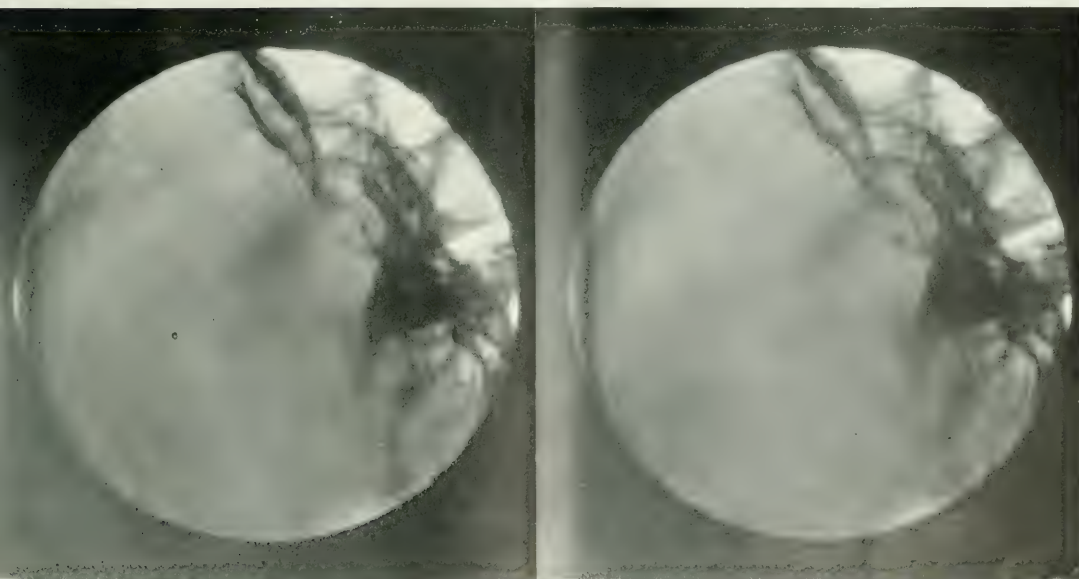


FIG. 7.—Roentgenogram of a patient with sarcoma of the optic nerve sheath. The small shadow appearing as a continuation upward of the posterior clinoid processes is an area of calcification in the tumor. The sella turcica is flattened.

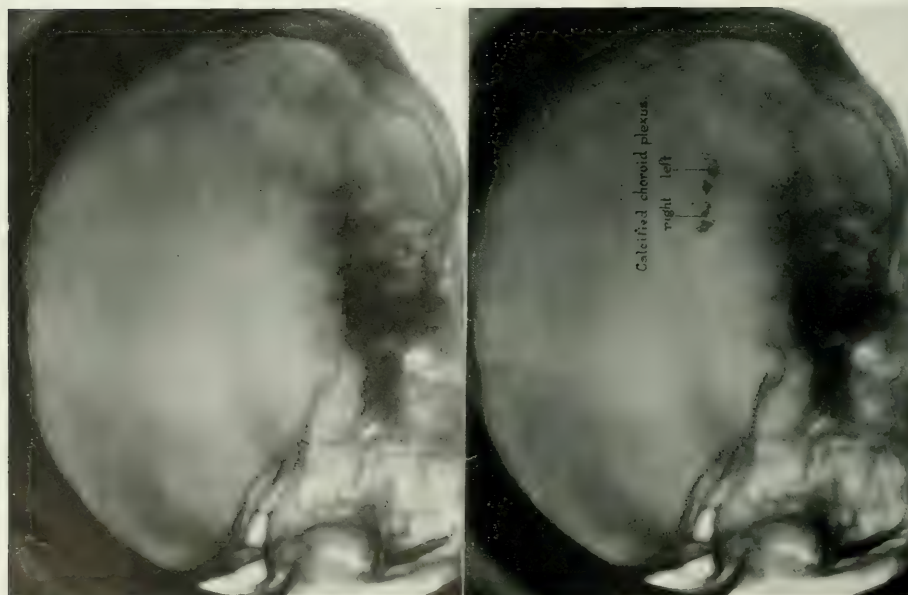


FIG. 9. Roentgenogram showing shadows cast by areas of calcification in the choroid plexus.

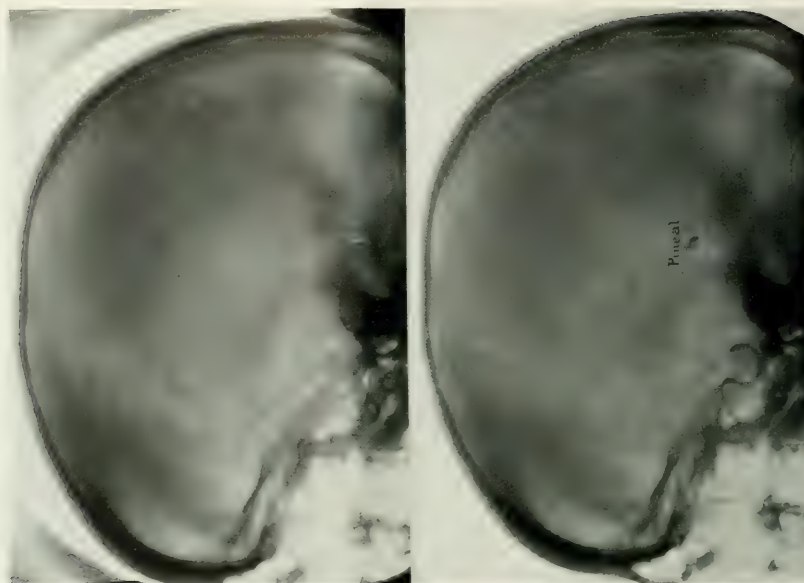


FIG. 10. Roentgenogram showing the shadow cast by an area of calcification in the pineal gland.

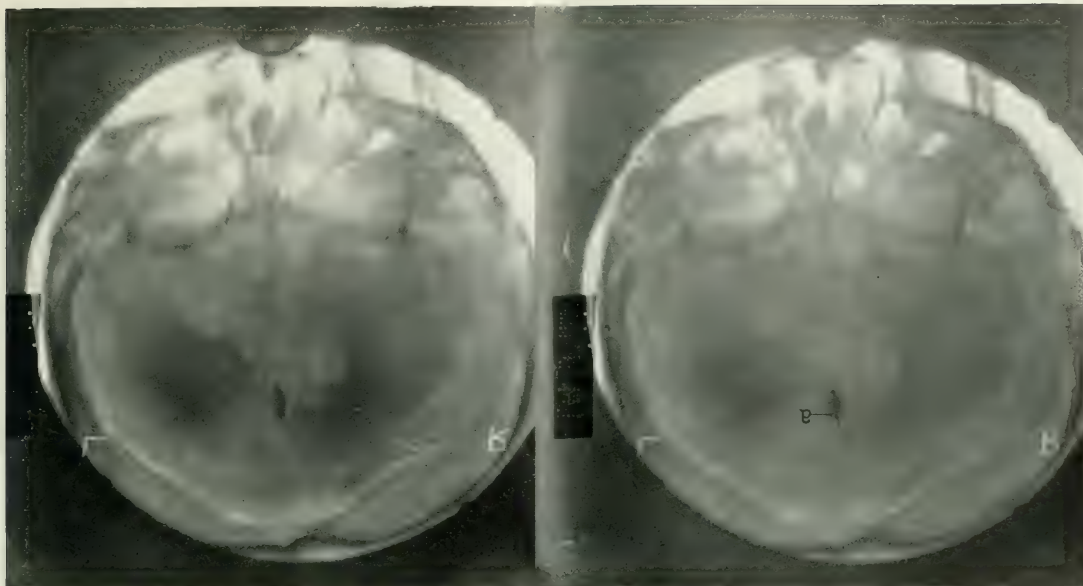


FIG. 11A.—Antero-posterior roentgenogram showing the shadow cast by an area of calcification in the falx cerebri.

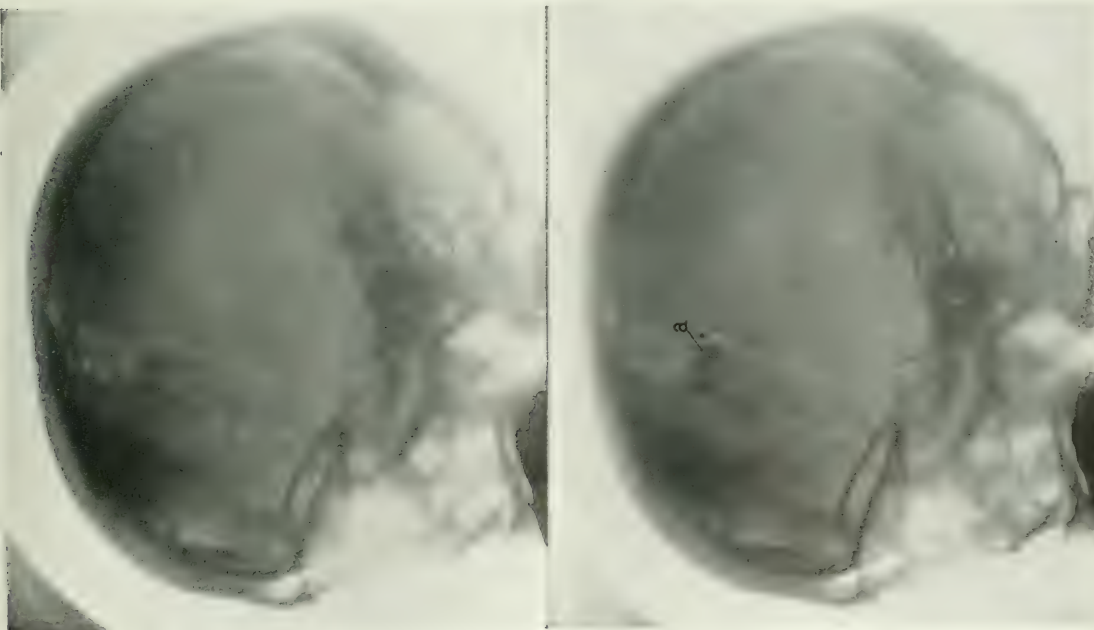


FIG. 11.—Roentgenogram showing the shadow cast by an area of calcification in the falx cerebri. The shadow might be mistaken for a tumor-shadow. Its position in the median plane is seen in Fig. 11A.

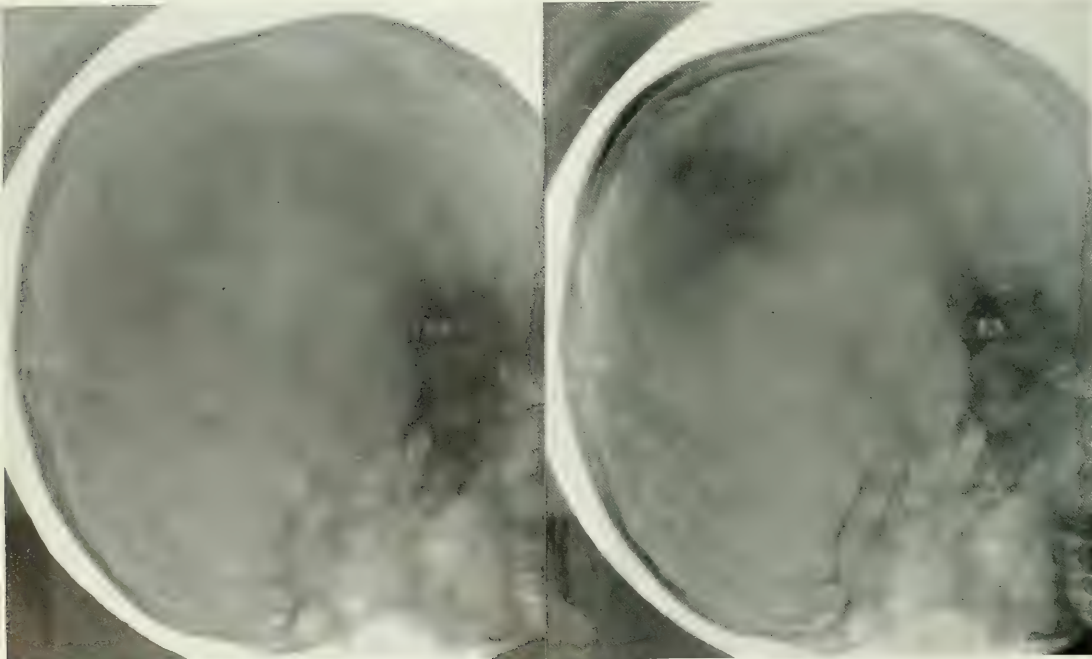


FIG. 12. Roentgenogram of a patient with cerebellar tumor, showing enlargement of the skull, separation of the cranial sutures, general convolutional atrophy, and partial destruction of the sella turcica. The enlargement of the internal auditory meatus is evident.

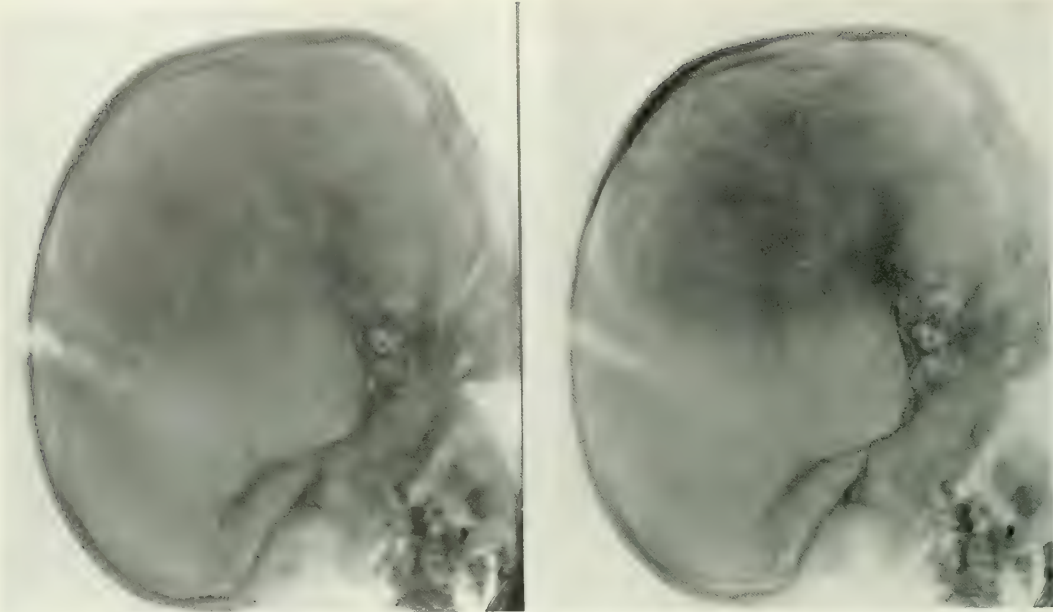


FIG. 13. Roentgenogram of a patient with cerebellar tumor showing enlargement of the head, wide separation of the sutures, and complete destruction of the sella turcica. There is no convolutional atrophy. The internal auditory meatus is enlarged.

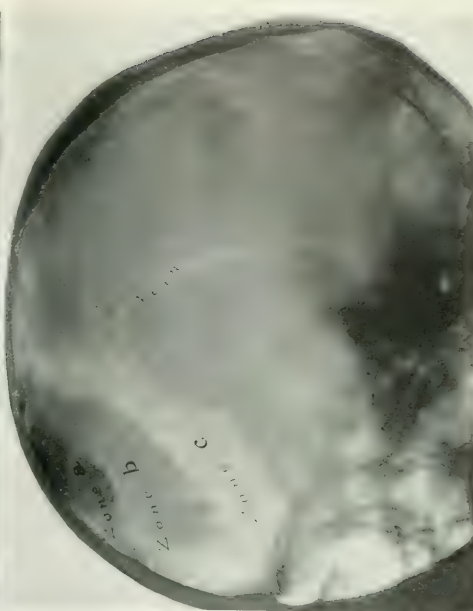
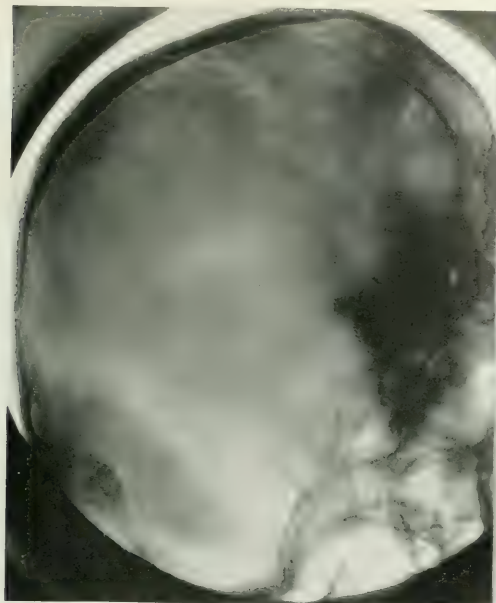


FIG. 15. Roentgenogram of a patient with a dural endothelioma in the frontal region, showing a marked hypertrophy of the skull over the tumor (zones *a* and *b*). There is atrophy of the skull about the area of hypertrophy (zone *c*). Note the single large vein with its branches.



FIG. 14. Roentgenogram of a child with "idiopathic" internal hydrocephalus, showing a general convoluted atrophy of the inner table of the skull.

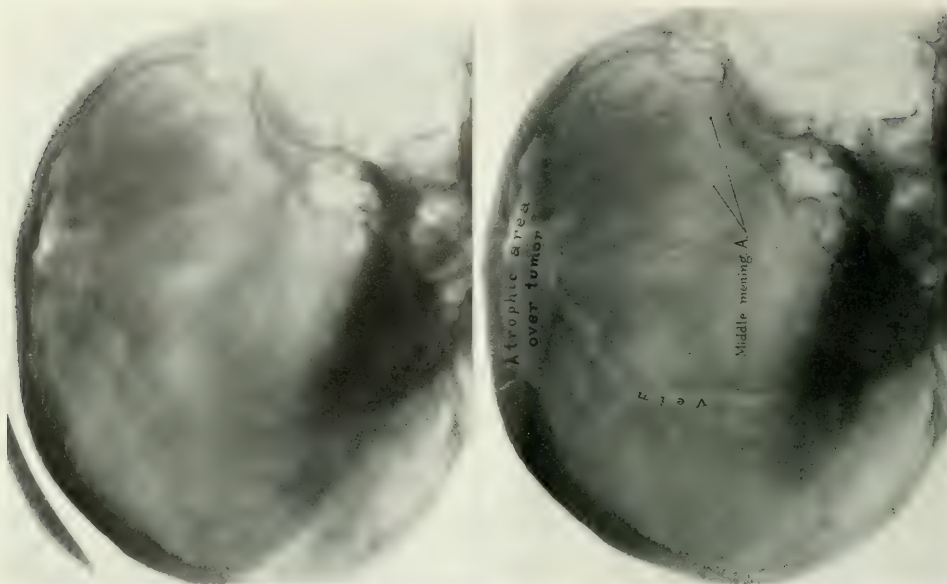


FIG. 17.—Roentgenogram of a patient with a dural endothelioma showing a local atrophy of the vault over the tumor. Note again the large vein (unilateral) coming from the region of the growth.

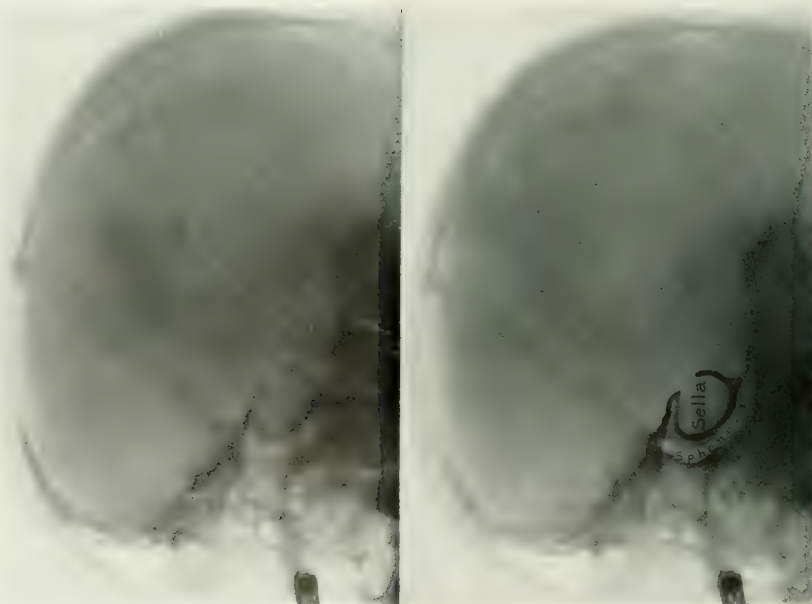


FIG. 16.—Roentgenogram of a patient with acromegaly, showing the local enlargement of the sella turcica without destructive changes and without alteration of the distance relations between anterior and posterior clinoid processes.

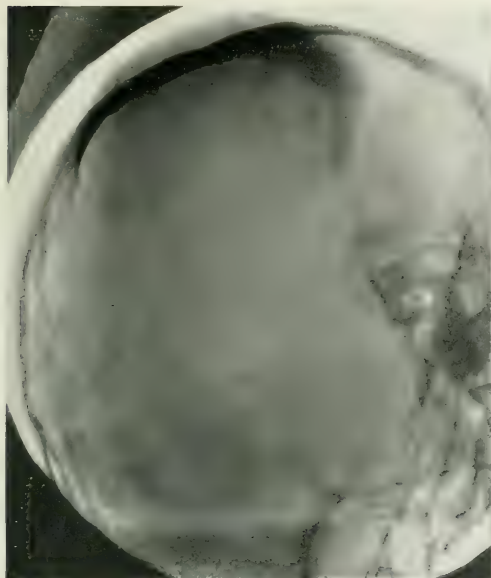


FIG. 19. Roentgenogram of a patient with a suprasellar tumor showing complete destruction of the sella turcica. Note the signs of increased intracranial pressure, i. e., convolutional atrophy and separation of the sutures.

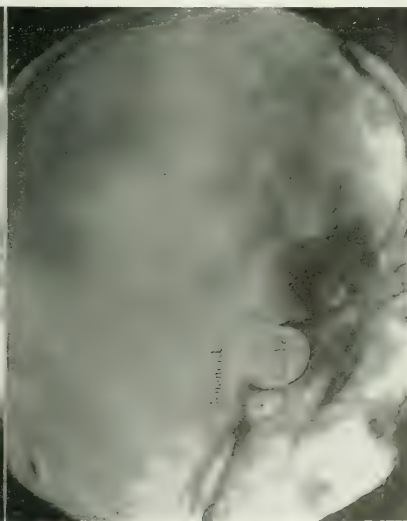
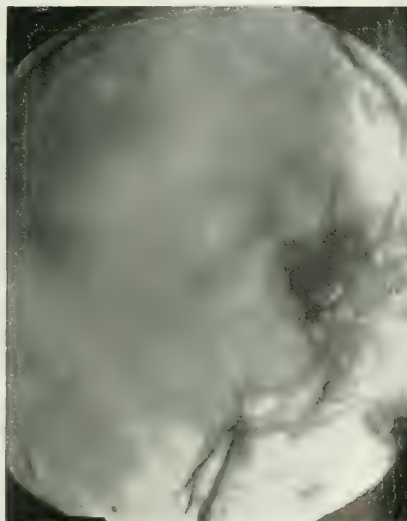


FIG. 18. Roentgenogram of a patient with a pituitary tumor showing the local enlargement and partial destruction of the sella turcica.

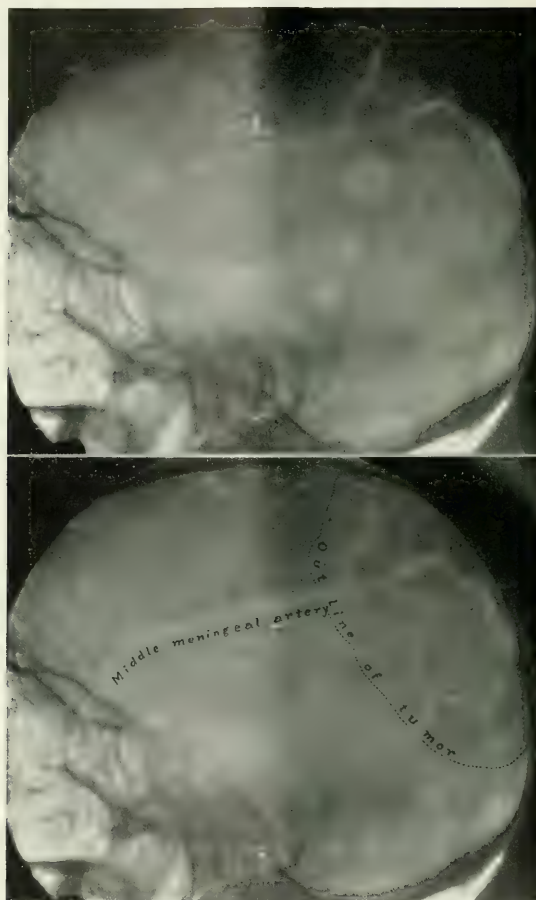


FIG. 20.—Roentgenogram of a patient with a dural endothelioma showing a marked unilateral enlargement of the meningeal artery. The outline of the tumor as found at operation is shown by the dotted line in the lower figure.

In so far, therefore, as the figures here presented approximate those reached by others in similar inquiries, we may safely accept them as indicating the trend, at least, which would develop in the analysis of like groups regardless of numbers.

The material here considered consists of 1,515 cases of tuberculosis, all except seven of which were pulmonary. All the patients were under observation and treatment in Loomis Sanatorium for at least one month (the average stay for the various classifications in different years being from six to nine months), scattered over the period from the opening of the sanatorium in 1896 to October 31, 1910. These cases were variously classified upon admission as follows: Incipient, 256; moderately advanced, 634; far advanced, 618; and seven with lesions elsewhere than in the lungs. The classification schema is the simple form of that of the National Association for the Study and Prevention of Tuberculosis.

This group of 1,515 patients was selected because, of the individuals comprising it, we have the following definite information: (a) We know that all were living at the time of discharge; (b) we know whether they were living or dead at the expiration of five years thereafter; (c) of the dead, we know at what period within the five years death occurred; (d) we know whether or not *B. tub.* was demonstrable in the sputa of these patients while they were in the sanatorium.

Much other information we have respecting this group, but for present purposes these four points suffice, and by limiting the inquiry we avoid that attenuation of numbers which further division would entail, and which, in the consideration of so small a group, would necessarily render deductions somewhat uncertain. There can be no ambiguity in the answers to these four questions. If, on the other hand, we attempt to subdivide the living into "Health satisfactory" and "Health unsatisfactory," we are dealing largely with patients' opinions, which may or may not be correct; but "Alive" or "Dead" admits of no qualifications.

Limiting the inquiry to a period of five years is perhaps more arbitrary. We know that many patients with chronic tuberculosis are alive five years after discharge from the sanatorium, notwithstanding that their disease is progressive, and that quiescence has never been established, nor is likely to be. But the advantages of choosing such a comparatively short period for such a study as this are several: (a) It suffices to indicate the trend through the most critical period; (b) it is the maximum period which would apply to all cases alike in this particular group; (c) it eliminates to some extent the element of an increasing death rate, from causes other than tuberculosis, incident to advancing age; and (d) it serves to convey more easily and graphically a mental picture of the life or death curves, and is therefore more practicable for an occasion like the present.

If we can estimate with any degree of accuracy the chances of life among the patients now under consideration for five years subsequent to their discharge from close observation and treatment, we have gone far toward establishing an ultimate prognosis; for, as will be seen by reference to the charts, the

death rate tends to become more nearly constant after the third year and probably would be still more so if the group comprised thousands instead of hundreds.

There is no intention in this brief study to argue for the sanatorium or any other method of treatment. Many of the group, especially among the far advanced class, had been under treatment, either at home or in resorts, both before and after their sanatorium experience.

The object here is rather to inquire what may reasonably be expected from intelligent care and treatment in various classes of tuberculous invalids, with the assumption, to start with, that a patient who will spend at least a month (in most instances many months) in a sanatorium will avail himself of every means of recovery within his reach, and with his sanatorium training will avoid, at least, the more dangerous pitfalls which beset the consumptive.

Proceeding then to an examination of the charts: Nos. 1, 2 and 3 are arranged to indicate in graphic curves the deaths among various classes of tuberculous patients during five years after discharge as compared with those among the general population; and Chart 4 is a table showing the chances for or

CHART 4.

COMPARISON OF ODDS FOR OR AGAINST PROBABILITY OF LIFE AT THE END OF FIVE YEARS.

	Number in each one thousand alive at end of five yrs.	Number in each one thousand dead at end of five yrs.	Odds for or against the probability of life at the end of five years.
General population.....	951	49	19.4 to 1 in favor.
Tuberculous patients by condition on admission.			
Incipient.....	859	141	6.1 to 1 in favor.
Moderately advanced.....	558	442	1.3 to 1 in favor.
Far advanced.....	222	778	3.5 to 1 against.
Tuberculous patients by condition on discharge.			
Apparently cured.....	919	81	11.3 to 1 in favor.
Arrested.....	662	338	1.9 to 1 in favor.
Improved.....	385	615	1.6 to 1 against.
Unimproved.....	50	950	19.0 to 1 against.
Tuberculous patients.			
No bacilli demonstrable during residence.....	874	126	6.9 to 1 in favor.
Sputum changing from bacillary to non-bacillary.....	773	227	3.4 to 1 in favor.
Sputum bacillary on discharge.....	287	713	2.5 to 1 against.
All classes of tuberculous patients combined.....	473	527	1.1 to 1 against.
Patients discharged with disease quiescent but with bacillary sputum.....	607	393	1.5 to 1 in favor.

against life during the five years among these various classes. In all the charts the various classes are considered on a basis of 1000 in order to facilitate comparison with the accepted figures for the general population, as well as with each other. The actual number of tuberculous individuals, however, is indicated at the termination of the curves in each of the graphic charts.

Chart 1 is plotted to show the death curves among patients classified as to their condition upon admission without reference to their condition upon discharge. It presents, graphi-

cally, the usual argument in favor of placing the patient under treatment at the earliest possible stage of the disease. It illustrates what might be expected with regard to far advanced cases and, to a lesser extent, the moderately advanced group, *i. e.*, the high death rate during the first two years after discharge, with a subsequent tendency on the part of the curve toward the horizontal. In this respect it corresponds, though in far less degree, with the curves of the improved and unimproved classes on Chart 2. These two charts, however, should not be compared one with the other, since they are dealing with such different groupings.

It will be noticed that the death rate in the incipient class, in contradistinction to the two other groups, increases after the second year, and the curve does not again trend toward the horizontal until the last year of the period. Although this group is so small, this peculiarity of the curve is probably not accidental, but is quite what might be expected. The progressive cases of the group classified as incipient naturally have a longer interval before the disease reaches a fatal termination than is the case with the more advanced classes. From a comparison of these curves it is possible to estimate roughly the relative length of life among those individuals of the several groups in whom care and treatment fail to arrest the disease. Turning now to Chart 4, we have, expressed in proportion, the chances for or against life five years after discharge from treatment, as applying to this grouping.

It must be borne in mind, however, that the mathematics of chance cannot be strictly applied here, but only in such measure as to furnish a reasonably safe basis for a broad comparison. For instance, in the far advanced class of tuberculous patients, the odds figure 3.5 to 1 against the chance of life at the end of five years; but this group is made up of individuals who were discharged, some apparently cured, some arrested, some improved and some unimproved. Obviously, it cannot be said that these odds will apply in general to the far advanced stage irrespective of condition on discharge; so that the figures are of value only as a means of comparing the far advanced group with other groups to which the same or similar restrictions apply. Nevertheless, it is probable that were the same grouping made from other reliable records and the same schema of classification employed, the results would approximate these fairly closely.

The variation in chances, as here shown, between the incipient and the far advanced classes is wide—6.1 to 1 in favor of life in the former as against 3.5 to 1 against life in the latter. These figures, as respecting the incipient class, I think will be found approximately correct and fairly safe for general application; but in the case of the far advanced, with our present crude schema of classification and the wide variation in condition of individuals that our present schema necessarily throws into this class, one would have to be much more guarded in expressing relative chances mathematically.

Chart 2, as you see, illustrates in graphic curves the history, for five years subsequent to discharge, of the same group of patients, but classified as to condition on discharge without reference to condition upon admission. In this chart it is

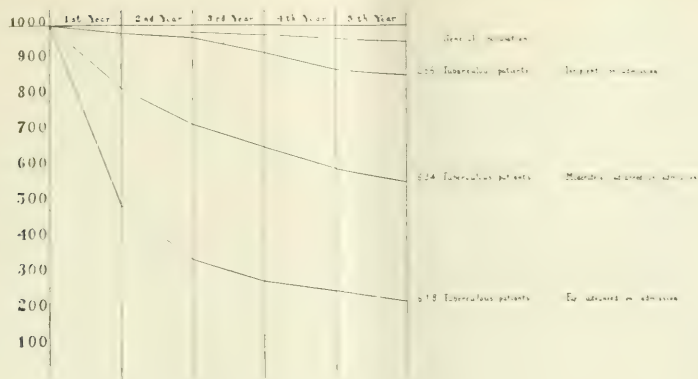
noticeable that the death curve in the apparently cured class differs very slightly from that of the general population—indeed, is parallel for the first year—and later diverges very gradually. If this class were made up exclusively of patients classified upon admission as incipient, the curve would approximate that of the general population even more closely, as naturally the “apparent cures” among the advanced classes are more prone to relapse. The curve as applied to the unimproved is spectacular, not to say shocking—76% dying within the year after discharge, and only 5% remaining alive after five years. These curves, I think, would be found to apply generally were similar classifications employed with other reliable data, and they serve to illustrate what may be expected for five years subsequent to discharge from modern treatment in a similar group of patients.

To turn again to Chart 4 for an expression in figures of the chances for or against life within the period considered, we find that the apparently cured enjoy odds of 11.3 to 1 in favor of life, while among the unimproved the chances against living are 19 to 1, or practically the same probability of dying within the five years as the normal population has of living for the same period. This chart argues one point which I think is worth remark, and that is the relative accuracy of our present plan of classification upon discharge. No schema of classification so far devised has proven wholly satisfactory; but, from a study of ultimate results, comparatively little fault can be found with this feature of our present schema.

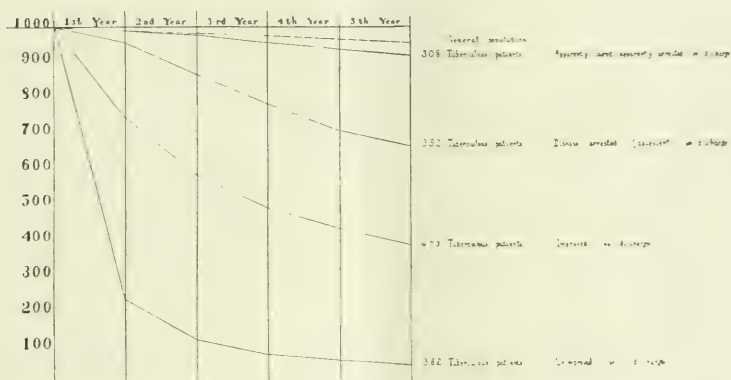
So much for prognosis as indicated in a study of the comparatively limited group of patients here considered. The charts speak for themselves within the restrictions imposed by the somewhat small number of individuals and the limited period of time which we have chosen. Comparing the results with those of other observers who have published records of similar groups considered in like manner, there is no wide discrepancy, and in so far the curves here presented may, I think, be very generally applied.

In the beginning of this paper I stated that, in addition to the question of prognosis, certain results of our inquiry had suggested a more definite objective in treatment than had hitherto appeared as such in any of the published reports with which I am familiar. Let me very briefly explain:

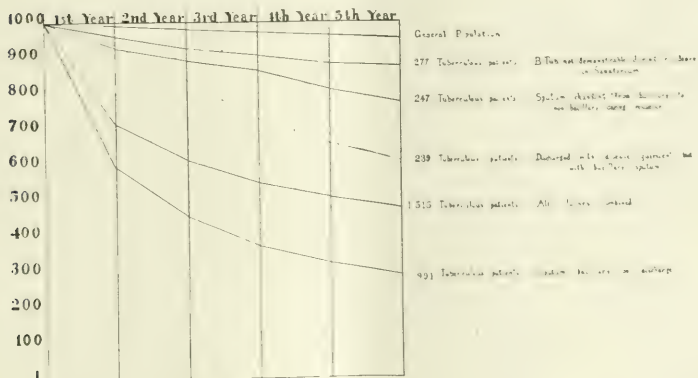
The great majority of patients who, for the first time, come under treatment in a sanatorium or in the open resort have but the vaguest idea of what specific thing they have come there to accomplish—to recover from tuberculosis, of course; but when told that the term “cure” is not now employed; that it is impossible to say with definiteness when an “arrest” has been achieved; that certain adventitious physical signs are not incompatible with “economic health,” so to speak; that slight cough and expectoration may persist through the remainder of their lives to remind them of their lesions, and that enormous weight-gain does not mean recovery in tuberculosis, it is quite natural, I think, for them to wonder just what criterion they are to employ to determine the length of their sacrifice and the period at which they may with greatest safety return to their normal occupations and home environment.



No. 1.



No. 2.



No. 3.

GRAPHIC CHARTS SHOWING DEATH CURVE OVER A PERIOD OF FIVE YEARS IN GENERAL POPULATION, AS COMPARED WITH THAT OF VARIOUS CLASSES OF TUBERCULOUS PATIENTS.

This has not been an easy question for the specialist to answer, much less for the family physician who has discovered the disease and sent the patient away. It may be somewhat disconcerting, but it is none the less a fact that comparatively few patients, outside of the incipient group, among the various classes going to make up the personnel of tuberculous communities, can or will remain under close observation and treatment long enough to become permanently arrested cases.

It therefore becomes almost necessary, nowadays, to hold out both to the patient and to the physician some definite objective, toward which the patient may look with some reasonable chance of achievement, as a goal the attainment of which will free him from the more irksome restrictions that surround him while under systematic treatment. In an article published some years ago by Noel Bardswell, which had to do with records of tuberculin-treated cases, attention was first drawn, so far as I am aware, to the importance of changing a lesion from an "open" to a "closed" one. This he considered the paramount and unequivocal sign of improvement. In the course of our inquiry at Loomis the great advantage of this attainment has been proved by the histories of such cases after discharge from the sanatorium; so that we have come to hold out this achievement as the most important single desideratum toward which the patient should direct his efforts, and for which he should exercise his patience and perseverance. It has the advantage of being definite; it is a question which can be answered categorically, and it seldom fails to appeal to the intelligence of the average patient, who will make the greater effort when he has a specific objective. Unfortunately, it is difficult of achievement in the more advanced cases within the limits of time which financial considerations usually permit a patient; but it comes more easily than does an apparent cure, and it is something which can be striven for and often attained after the patient has resumed his normal vocation and environment.

Chart 3 is plotted to illustrate the foregoing argument. It is made up of the same group from which the other charts were constructed, and is, like them, self-explanatory. The patients discharged as non-bacillary are, as will be noticed, separated into two sub-groups, which separation, while it attenuates the numbers, does away with the objection that might otherwise be raised regarding such cases as were never found to be bacillary. Bear in mind that, of the sub-group changing from bacillary to non-bacillary, there can be no ambiguity as to diagnosis, and that many in this division were discharged with no better classification than "arrested"—some merely "improved" and a few "unimproved." With these points in consideration, a comparison of the several curves shows unmistakably the advantage in prognosis which the loss of bacilli gives a patient. Obviously, it would not be fair to compare the death rate in the non-bacillary class or in the class losing bacilli during treatment with the class discharged "bacillary," since the latter would include all of the progressive cases discharged "unimproved," in which, as we have seen, the prognosis is very bad. In order, therefore, that we may have two approximately comparable groups,

another sub-group has been formed. It is indicated on the chart by a dotted line and comprises patients all of whom were discharged with disease "arrested," but with bacillary sputum; while in the group with which it is to be compared, all of whom were discharged without bacilli, there are unavoidably included a few patients who left the sanatorium only "improved" and some "unimproved"—a small, unfavorable element which accounts for the apparently anomalous and slightly greater death rate in the non-bacillary class during the first year as compared with that in the "arrested" bacillary group. The "improved" and "unimproved" in the non-bacillary group would naturally be nearly all eliminated during the first year.

A comparison, now, of the curves under discussion is, I think, very convincing of the advantage of becoming non-bacillary, and seems to justify the contention that, short of an "apparent cure" of the disease, with all that the term implies, the achievement of a "closed" lesion is the chief definite objective for which the patient and his physician should strive during the months of what might be termed the "active treatment of the disease."

For the interesting charts and statistical figures upon which this study is based I am indebted to our statistician, Mr. Cornelius W. Dever and to Mr. Raymond P. Woodman of the Loomis staff.

DISCUSSION.

DR. LOUIS HAMMAN: I have listened with much interest to Dr. King's presentation. On a number of occasions I have gone over reports upon large numbers of tuberculous patients and I appreciate fully the value of a study of this kind made upon patients who have been observed and classified in a uniform way. Most statistical studies of tuberculosis handle material gathered from various sources and arranged and judged by different standards. Large figures are imposing, but one familiar with the methods of observing and classifying patients will at once appreciate the possibility of grave error. Statistical studies comprise two parts, the medical data upon which the figures rest and the mathematical manipulation of these figures. The latter part is developed into an exact science, but all of this exactness is wasted if the medical data are inaccurate and unsatisfactory. Therefore, a small group of cases observed by one man, or at least in a single institution with permanent traditions, is of far greater value than elaborate mathematical computations of material gathered from various and varying sources.

I recall one occasion when I tried to gather convincing figures to demonstrate the value of our tuberculosis campaign and to discover those measures of the campaign that had given the largest benefits. It was interesting to find observers drawing different and often opposed conclusions from the same figures. And another occasion when my object was to reveal the value of tuberculin treatment. Although numerous studies were at hand, I was surprised to find upon close analysis that the most enthusiastic reports often dwindled to personal impressions. I was convinced by the investigation that the only standards of value were whether the patients were living or dead at the end of a certain period, and the disappearance of tubercle bacilli from the sputum. I am pleased to note that Dr. King also has emphasized these two standards.

Frequently in discussion before this society I have called attention to the difficulties surrounding the diagnosis of early or incipient pulmonary tuberculosis. The diagnosis of incipient tuberculosis for purposes of treatment and for purposes of sta-

tistical study is widely different. In the one instance we are concerned with the safety of an individual; in the other our object is to ascertain the truth shorn of personal considerations. Standards of diagnosis do vary and always will in such an uncertain field. I need merely mention the difficulty of distinguishing active from inactive lesions. To be absolutely reliable statistical studies of pulmonary tuberculosis should include only patients with tubercle bacilli in the sputum, and since so small a proportion of patients with bacillary sputum are in the incipient group it follows that at the present time a satisfactory statistical study of the incidence and course of incipient pulmonary tuberculosis is beyond our reach. I am quite sure it is beyond our reach, and I am also sure that some of our impressions about this group are so strongly flavored with the personal equation that they savor of error. The strikingly favorable course of Dr. King's incipient cases raises the question about the diagnosis in this group. I know Dr. King will at once admit the possibility of error and at the same time insist, as I do, upon the impossibility of doing any better at the present time.

In the end prognosis must aim to be individual, that is, not only to tell the chances of life in a group, but to say what will happen to a particular patient. This is the ultimate refinement of the art towards which we strive. In the meantime, such careful studies as Dr. King has made carry us slowly towards the goal.

DR. H. B. JACOBS: I am struck with the value of these charts for use as tuberculosis propaganda. It is so difficult to get patients early enough. They do not appreciate the tremendous importance of losing no time in the beginning. If we could have such charts

as these published to bring to the attention of those who are having an unremitting cough, it seems to me we might have in them means of impressing such with the value of early treatment as has not been found before.

DR. H. M. KING: I quite agree that the ultimate object in prognosis is to apply it to the individual. "Group" prognosis, so to speak, while it has a very distinct value, falls short of the requirements. It does not satisfy to say that a certain percentage of such-and-such a group recovers. One should strive to recognize the factors which go to determine the prognosis in the individual and then to apply the knowledge to the individual. As has been said, prognosis is a science, only we have not treated it as such. A study like this is but a step toward placing it where it belongs. Much remains to do—further statistical inquiry and a great deal of laboratory investigation—before we may venture individual prognosis in tuberculosis with confidence or assurance; but I do think we are now proceeding along right lines.

As to the question which Dr. Hamman raises regarding diagnosis in the incipient class, I think it is true that not a few cases remain under observation and treatment for months, classified as positively tuberculous, in which the one unequivocal diagnostic factor is lacking, namely, the presence of *B. tub.* in some of the excretions; and among these cases doubtless there are some, perhaps many, which, if the truth were known, are not tuberculous at all. For this reason I thought it well to separate the group of cases in which *B. tub.* had at no time been demonstrated, a group which, as you see, comprises 277 cases, some of which I have no doubt never had tuberculosis.

THE RENAISSANCE OF UROLOGY.¹

By HUGH HAMPTON YOUNG, M. D., Baltimore, Md.

I have chosen as my subject the Renaissance of Urology. In explanation I may say that urology, comprising as it does the diseases of the urinary tract, was perhaps the very first branch of medicine to emerge from the clouds of ignorance in prehistoric times. This probably came about from the fact that when urination became painful, difficult or impossible, the male being was driven to that desperate necessity which is the mother of invention.

Thus, among the ancient Hindus, probably over a thousand years before Christ, we find the catheter used to relieve retention of urine; the sound to dilate strictures of the urethra, and the operation of perineal lithotomy fully developed and widely practised.

Sucruta's manuscript giving us details of the operation of lithotomy was written about B. C. 600. It is interesting to note that the perineal operation for stone, which is so skillfully performed by the native lithotomists of India to-day, is practically the same as that described by Sucruta 2500 years ago.

In the writings of Hippocrates (B. C. 460) we find accurate descriptions of the formation of urinary calculi, of lithotomy and of nephrotomy; and this at a time when practically no other operations upon abdominal viscera were attempted. The history of major surgery may, therefore, be said to have its beginnings in the work of the early urologists, and to owe its inspiration to them.

By the Hippocratic oath the general practitioner of medicine was required to promise never to perform lithotomy, but to leave the operation to those who made a specialty of it—the so-called lithotomists.²

Celsus shows by his writings at the beginning of the Christian era that operations for calculus, retention of urine and urinary fistula, were well developed; and Galen (B. C. 130-210) and Aurelianus (B. C. 300) describe certain progress in urology; but during the long years of the middle ages "while medicine was in the hands of the monks who disdained surgical operations," the "Lithotomists" alone kept up the surgical spark. During this time certain inhabitants of the town of Norcia developed such skill in lithotomy that they were called to all parts of Europe, and were frequently official employees of municipalities where they attained great fame, thus being the first public health officers.

The operation for stone, which had thus far been entirely in the hands of these itinerant laymen, was finally adopted by the medical profession through the work of Germain Colot about A. D. 1460.³ Colot was a French surgeon of renown. Declaring it a disgrace that an operation of such importance should have been so entirely neglected by surgeons, he went to Italy, ingratiated himself with a family of lithotomists, learned their methods, and then returning to France, instituted a series

¹ Oration on Surgery. Southern Medical Association, Ninth Annual Meeting, Dallas, Texas, November 8-11, 1915.

² See Guitéras: The Evolution of Urology, N. Y. Med. Jr., Oct. 11, 1902, which has been freely quoted.

³ Fisher: Annals of the Anatom. Surg. Soc., 1880.

of experiments upon the cadaver, the results of which he reported to the Medical Faculty of Paris, and at Court. He then applied to King Louis XI, who granted him permission to operate on a criminal condemned to be hanged.

It is interesting to note that this historic operation, which was carried out in the presence of the King, was performed in the churchyard. The patient showed great fortitude, was well in two weeks, and saved his own life, besides saving the lives of future generations by securing this operation to surgery.

Colot was decorated by the King, appointed the Royal Lithotomist, and became the father of a family who furnished France with its chief lithotomists for three hundred years. Although medical men, they kept the secret to themselves just as the Norcians had done, and were consequently reviled by the rest of the profession until François Colot, the last of the family, gave the secret to the medical world in 1727.

The general surgeons, however, seemed unable to make a success of lithotomy, which was still the gravest and most difficult operation in surgery, so that again non-medical operators flourished—the chief of whom was a monk named Frère Jacques who, marvelous to relate, invented and introduced the lateral operation for stone, which requires far more precision and expert knowledge of anatomy than the median operations previously used. The story of Frère Jacques, his meteoric rise at court, the crowds that assembled to see his lightning-like procedures, his admission to the great hospitals of Paris over the protest of the surgeons, and his final departure in disgrace because most of his patients died, is one of the most thrilling histories of surgical literature.

Although discredited in Paris he evidently flourished elsewhere, as he is said to have cut more than five thousand for stone, and often to have operated upon sixteen patients in one afternoon. He died in 1720, and his operation, perfected by the great Englishman Cheselden, is notable as being based on the finest anatomical principles, in that it avoids injury to such important structures as the external sphincter, the cavernous tissues of the bulb, and the crura of the penis, thus preventing incontinence and sexual impairment.

To this day the non-professional lithotomist exists in the East; and even in Scotland, only a century ago, Mr. Adams stated that "there was an old miller who was very famous for cutting persons for the stone." For some inexplicable reason the major things in surgery were largely left for uneducated operators—even Ambroise Paré was a blacksmith. Paré learned lithotomy from a Colot, and was one of the most accomplished in its performance.

My prolixity on this subject is due to my desire to point out surgery's debt to the ancient and mediæval urological specialists who, almost alone, kept going the flame of major surgery when the forces of religious and medical superstition would have extinguished it. Indeed it was not until John Hunter came that the solid foundations of scientific surgery were laid. It is interesting to note that at that time there were only two great surgeons in England, William Cheselden and James Douglas, both of whom owed their reputation chiefly to their operations for stone. Hunter became the pupil of one of these,

Cheselden, the originator of the present "lateral operation for stone," which he was able to perform in 54 seconds.

It is probable that this association with Cheselden, the foremost urologist of his day, inspired Hunter to undertake his masterly researches on genito-urinary diseases, and to collect at such great pains the wonderful specimens of urinary disease, particularly of calculus, enlarged prostate and kidney, which form the most striking and valuable part of the pathological work left by him. It is very evident, from a study of the clinical works of Hunter, that his private practice was largely genito-urinary in character. It was Hunter's practice to admit young men into his home for a long period of years as private students of surgery, and it is not surprising to find that of these men who afterward became famous, and caused English surgery rapidly to eclipse the rest of the world, the majority were particularly interested in genito-urinary surgery. I need only refer to John Abernethy's celebrated treatise on syphilis, Sir Astley Cooper's classic on the testicle, Sir Everard Home's two volumes on the hypertrophied prostate gland, and James Wilson's anatomical researches on the external urethral sphincter.

The history of urology in France during the eighteenth and nineteenth centuries, as in England, contains the names of almost all the celebrated surgeons, for here again it was the most difficult and dangerous surgery performed. Commencing with Guy de Chauliac, we find Colot, Paré, Dionis, Le Dran, Desault, Dupuytren, Nélaton, Chopart, Civiale, Leroy, Heurteloup, Mercier, Maisonneuve, Guyon, Pousson and Albarran. The most important invention of this time was that of stone crushing by Civiale, in 1818. This subject was further developed by Leroy, Heurteloup in France, and by Thompson and Weiss in England. Mercier's work on obstruction at the vesical neck, and the ingenious instruments he devised, were of great importance; but to Civiale first, and later to Guyon, the medical profession owes most of the solid foundation of urology upon which so wonderful a superstructure has lately been reared.

Sir Henry Thompson, in England, a brilliant pupil of Civiale, pursuing the careful research methods of John Hunter in anatomy and pathology, did more perhaps than any one man in the nineteenth century to bring urology into the very forefront of surgery, and to inspire men to devote their lives to this special branch.

While the school of Thompson in England, and that of Guyon in France, were increasing in vigor and force in the latter part of the last century, America and Germany had awakened and were fast becoming powerful factors in the rapid advance.

Early in the past century America developed a remarkable coterie of lithotomists. The greatest of these was Dudley of Lexington, Kentucky, who had the remarkable record of 207 cases with only 6 deaths—1 in 34½, or less than 3%—Valentine Mott, the greatest New York surgeon, had 7 deaths in 162 cases, and Nathan R. Smith of Baltimore 3 deaths in 45 cases. In a recent volume, "Kentucky Pioneer Lithotomists," Dr. A. H. Barkley tells of the wonderful work done by McDowell,

Dudley and Bush. McDowell learned lithotomy from John Bell in Edinburgh, in 1791, and had 28 cases without a death. Dudley, who followed him, was a student of Sir Astley Cooper in London, in 1813, and had only 3 deaths in 225 lithotomy cases, according to Barkley, and one series of 100 cases without a death—a record which has never been equaled. Bush worked with Civiale in Paris, in 1839, and became America's foremost litholopaxist. These three surgeons, all residents of Lexington, Kentucky, and occupying the same office, formed one of the most remarkable medical groups in America. The total for the United States, as collected by Gross in 1850, was 851 cases with only 1 death in 20; whereas, according to Coulson, in Europe the proportion of fatalities was 1 in 5.

The greatest of all American surgeons, Samuel D. Gross, was himself an eminent lithotomist, and his principal work, "Diseases of the Bladder, Prostate and Urethra," published in 1850, still ranks as a classic. Although a professor of general surgery and a prolific writer on many subjects, his most brilliant work was in urology; and he may really be said to be the father of American urology, though Van Buren and Gouley, and later Otis and Keyes, of New York, and Bigelow, of Boston, exerted a more continuous influence. These men were the peers of the European urologists, and by their original contributions soon placed America in the forefront. Bigelow's classic researches on lithotomy challenged the admiration of the world and revolutionized the treatment of vesical calculus. Each of these men surrounded himself with ardent young fellows who have since formed the New York, Boston and Philadelphia "schools" of urology.

Austro-Germany lay dormant during this period of great activity in England and France, until the latter part of the last century, when Simon at Heidelberg began his epoch-making work on the kidneys. A young woman with a ureteral fistula appealed to him for relief. The only possibility of cure lay in removing the kidney; but no one knew whether life with only one kidney were possible. Could the repair of the renal artery ligated so close to the great aorta stand the pressure after absorption of the ligature? Might not emboli or peritonitis bring on early death? No one knew. In order to find out, Simon nephrectomized 30 dogs, and thus not only put the operation on a sound basis, but led the way to animal experimentation which has revolutionized surgery in recent years (another debt of surgery to urology). The operation was then carried out on the patient with perfect success in July, 1869. The great Bruns carried out the same procedure two years later with, however, a fatal result, and the next patient of Simon himself lost her life. The tragic story of this case is so beautifully told by Pilcher* that I cannot refrain from giving it again.

The patient was a brave little woman of Savannah, Georgia, who was sent across the Atlantic to Simon to be cured of a calculus pyonephrosis. "All previous authority had condemned such a procedure; never before had it been attempted, not until the operation was happily finished did the appre-

hension leave him that he (Simon) might yet find himself confronted by the conditions which his predecessors had described as unsurmountable. For three weeks the convalescence proceeded without disturbance, and the wound had contracted until it was now insignificant. Simon, however, shared in that spirit of the older surgeons, which prompted them to examine the cavity with their own fingers. They called the practice training their *tactus eruditus*. No unfortunate patient could have a cavity opened or a wound made without the bystanding surgeons being invited to put their fingers into it—the omission was a breach of professional courtesy. The boldness and enterprise of this Heidelberg surgeon had carried him further than most surgeons. He had passed his hand and forearm through the anal sphincter, and along the large intestine until he could feel the kidneys and liver of his patient: he had made a practice of dilating the female urethra with his forefinger which he carried into the bladder and by it guided a catheter into many a ureter (thus becoming the first to do ureteral catheterization). Where his fingers had been previous to his approach to the bed of his now fully convalescent nephrectomized patient, on this her twenty-first morning after the operation, who can say? The vexed question of antiseptics, rubber gloves, and surgical cleanliness had not yet begun to trouble the surgical mind. So much the worse for this little woman from Georgia, and her dreams of future health. As the dressings were being changed, the temptation to explore was too great, and in went his finger. Within a few hours came a chill and fever. For 10 days the battle between the body cells and the invading micro-organisms continued, and then death!"

Had Simon only heeded Lister, who four years before had published his great work on antiseptics (1867), the result might have been different. A similar fatal case of nephrectomy for calculus, in the hands of the great Von Bruns, put an end to kidney surgery for some time, and as late as 1879 Pilcher was able to find only 15 cases in the literature. But Lister's teachings had at last found an audience, and renal surgery was among the first of the great fields of major surgery to feel its influence. In 1885 Samuel D. Gross, in one of the most masterly clinical analyses ever made, collected 450 different operations on the kidney, and placed the whole subject on an enduring basis.

The next great advance in urology came from Austria—I refer to the invention of the cystoscope by Nitze in 1876. This instrument, which could not be perfected until Edison in 1879 brought forth the incandescent electric bulb, has not only revolutionized urology and brought it from darkness into light, but also has done more than any one invention to stimulate exactness in diagnosis, and the use of electricity in medicine.

Truly marvelous are the instruments which followed in steady succession. The ureteral catheterizing cystoscope, the operating cystoscope, the photographic cystoscope, the stone-crushing cystoscope, the fulgurating cystoscope, the rongeur cystoscope, the cauterizing cystoscope, the urethroscope, the bar-exercising endoscope, the laryngoscope, the otoscope, the gastroscope, the proctoscope, and electric ophthalmoscope, need

* Annals of Surgery, 1900, vol. 31.

only to be mentioned to indicate the tremendous activities which have been evoked by the development of the first cystoscope. In this great advance the geniuses of Germany and America have shared honors about equally. The great desideratum, catheterization of the ureters in the male, which had been looked forward to longingly but vainly for generations, was finally accomplished by an American, my predecessor at The Johns Hopkins Hospital, Dr. James Brown; and another Baltimorean, Howard A. Kelly, made ureteral catheterization in women possible and easy, and led to the brilliantly rapid evolution of renal and ureteral surgery that immediately followed. Time will not permit me to do justice to other American confreres who have done so much for this subject—Tilden, Brown, Otis, Belfield, Koch, Valentine, Lewis, Buerger, McCarthy, Squier and others.

It is important, however, that I refer to the great diagnostic methods that have been evolved as a result of the ureteral-catheterizing cystoscope. The mere separation of the secretions of the two kidneys was a great step in advance, enabling one to recognize the diseased kidney and to discover early tuberculosis, unilateral hematuria and, with the development of the X-ray and pyelography, various hitherto unrecognizable lesions. But it did not offer sufficient evidence concerning the other kidney. It did not remove that old dread that the remaining kidney might be unequal to the task of sustaining life when its fellow had been removed. For almost 20 years surgeons have been searching for an ideal functional test of the kidneys, and various drugs, generally dye-stuffs, have been brought forward. Casper and Richter, who introduced the phloridzin test, deserve great credit for impressing upon the profession the need of functional tests, although their phloridzin test proved unsatisfactory. The ideal test seems now to have been discovered: I refer to the phenol-sulphone-phthalein test, the result of the work of four of my *confrères* on The Johns Hopkins Faculty—Professor Remsen, who discovered the drug, Professor Abel, who showed that it was almost entirely eliminated by the kidneys, and Dr. Rowntree and Dr. Geraghty, who proved its clinical value by a long series of experimental and clinical researches.

Thanks to this splendid example of co-operative and consecutive effort between various departments, we now have an accurate method of determining factors of safety in renal surgery, and are in a position to know beforehand what should be done, and whether it is safe to do it.

A glance at the mortality figures during the past 30 years will show the transformation which the cystoscope, the ureteral catheter and the functional test have accomplished in kidney surgery. Gross, in his collection of 450 cases, found the mortality for nephrectomy for various diseases to be between 20% and 60%. In America now it is between 1% and 5%.

The Prostate.—The surgery of the prostate was even later in its development than that of the kidney. Although Covillard in 1638 removed an hypertrophied lobe after perineal lithotomy, Sir Henry Thompson, whose researches on the anatomy and pathology of the prostate are still classics of great value, stated as late as 1887 that successful prostatectomy was unknown.

It is almost tragic to hear this great urologist say: "I desire extremely to see such a result; I have on four occasions removed considerable portions of the prostate, but without success. I have traveled considerable distances abroad expressly seeking it, but without success." But at the time that he was writing younger forces were at work, and as a result of the cumulative efforts of Belfield (1887), McGill (1889), Goodfellow (1891) and Fuller (1894), prostatectomy became an established operation.

More accurate methods, based on anatomical landmarks and pathological studies, have greatly improved the perineal operation, so that the mortality rate which was 15% 20 years ago, has fallen to about 3% for conservative perineal prostatectomy in our clinic. In a recent study of 775 cases, I found 30 deaths, or 3.8%. Only eight deaths occurred within the first week after the operation, and 10 after a month. These figures show how benign prostatectomy can be made.

The careful study of cases, particularly as regards the kidneys, has had even more to do with the lowering of the death rate than a carefully planned anatomical operation. An early recognition that a large residual urine was a danger signal, especially if the patient had never been catheterized systematically, enabled us to so reduce the operative risk that it was possible to operate upon 128 consecutive cases without a death. Now that we have shown that the phthalein test gives an accurate index to the state of the kidneys, a means of determining when the operation may be safely performed is at hand, and with careful preparatory catheter treatment makes it possible eventually to operate on almost every case. One of our recent patients was 93 years old.

One of the most important urologic problems of the day is cancer of the prostate, which is now known to occur one-fourth as often as hypertrophy. It shows itself in early cases as a localized, very hard area in the posterior portion of the prostate, and if routine rectal examinations were made many early cases of cancer of the prostate would be detected. Ten years ago it was supposed to be beyond surgical relief. Now we have a well-established radical procedure in which, although the whole of the prostate, the seminal vesicles and the neck of the bladder are excised, the anastomosis between bladder and stump of membranous urethra can be so effectively made that neither stricture nor incontinence follow.

We have now apparent cures in 10 cases of cancer of the prostate—most of them over five years', and one of 10 years' duration—the percentage of cures being about 65. I predict a great future in cancer of the prostate.

Time does not permit to mention more than a few of the conquests of urology, but I must say a word in regard to the epoch-making advances that have been made in the treatment of vesical tumors. Even five years ago all statistics of results after operative excision of bladder tumors, both benign and cancerous, were so bad that Watson was boldly proposing cystectomy—complete removal of the bladder for almost all bladder tumors. The remarkable results obtained by Nitze with his cystoscopic cautery snare had been lost sight of. Then came Beer's report on the use of the high frequency electric spark, which causes most papillomatous tumors to disappear as

if by magic, and the statistics of results were transformed. When one sees a bladder half filled with sessile papillomata, each the size of a small walnut, become normal with not even a scar to show the site, one realizes that a wonderful therapeutic agent has been discovered.

Radium, too, is a force of marvelous power, the limits of which are little known, but which occasionally works seeming miracles. We have been using radium by means of special radium-carrying operative cystoscopes, in conjunction with the high frequency treatment of vesical tumors, and prostatic carcinomata, with really promising results.

The surgery of the seminal vesicles has also made rapid strides. Fuller deserves much credit for the persistency by which he has finally impressed upon the medical profession the important rôle of chronic infections of the seminal vesicles and prostate in the etiology of rheumatism, arthritis and heart disease. His operation of drainage of the seminal vesicles has accomplished wonders in curing hitherto intractable "rheumatic" infections. Recent improvements of the perineal prostatectomy technique have been applied to vesiculectomy and vesiculectomy, and made them accurate procedures under visual direction, removing all guesswork. I have extended this operation recently to the complete excision of tuberculosis of the seminal tract with the result that it is now possible to remove entirely extensive tracts of tuberculous infection, which were previously beyond surgical relief, and with the same splendid results which have followed nephrectomy for tuberculosis. It is no longer necessary to relegate these sufferers with seminal tuberculosis to a life of slow torture and ultimate death, for many will get well after excision of the entire infected genital tract, just as nephrectomy with ureterectomy has been shown to cure tuberculosis of the urinary tract.

Litholapaxy, which was the great contribution of America over a quarter of a century ago, has been simplified and facilitated by the invention of the evacuating lithotrite of Chismore, and the addition of the cystoscope has now made it possible to crush, evacuate, cystoscope and pick up a remaining fragment, all with one introduction of the instrument. The use of the median-bar excisor, or "punch," makes the cure permanent by removing the small bar or contracted vesical orifice, which in the past has been such a fertile cause of calculus recurrence.

I have already referred to the marvelous array of cystoscopic instruments which have been invented. It is now possible with the catheterizing cystoscope not only to collect the separated kidney urines, but to dilate strictures in the ureter, to facilitate the passage of calculi or even fracture them with electrical ureteral sounds, and to fill the ureters and kidney pelves with thorium nitrate, and thus obtain x-ray photographic demonstration of various lesions which were formerly hidden. The operative cystoscopes make possible the removal of cysts, tumors, specimens, foreign bodies and prostatic lobules, the division of strictured ureteral orifices, and the removal of small calculi from the ureteral orifices and from diverticula. Urology possesses unquestionably the most perfect diagnostic instruments and laboratory methods in the entire field of medicine and surgery. But what has brought

about this splendid achievement in accurate diagnosis and skilful operative relief? First, the fact that high class surgical work requires high class mechanical and technical men, and, if possible, personal training and skill in such by the operators themselves. With the mechanical talent, ability as draughtsmen to convey one's conceptions and ideals goes hand in hand, and a survey of the literature shows many remarkable instances in which mechanics or art, or both, were developed to a marked degree in the great men of medical science. I need mention only a few: Vesalius, the father of anatomy; Ambroise Paré, the father of surgery; Karcher, the inventor of the microscope; Cheselden, the great English surgeon, who designed Putney Bridge; Scarpa, Henle, His, Charles and John Bell, Leidy and Lister, all of whom illustrated their own works with beautiful drawings; Charcot, the great neurologist, and Seymour Hayden, one of the greatest painter etchers of all time, as well as a great surgeon.

Urology, probably more than any other specialty, owes much to mechanics and art in her devotees. The four moderns who have done most to develop the science are Nitze ("der grosse Techniker"), Henry Thompson, Henry J. Bigelow and Felix Guyon. All of these epoch-making men were great mechanics, inventive geniuses and idealists, whose spirits were never satisfied with the existing order, but constantly strove for perfection of detail, as well as broad advancement in the field.

The second factor in the modern advancement in urology has come about as a result of a closer co-operation between clinic and laboratory; for there is no branch of surgery which offers greater field and opportunity for varied laboratory work than urology.

A recognition of this fact led us, when preparing the plans for the James Buchanan Brady Urological Institute in Baltimore, to provide a most varied assortment of laboratory and research facilities presided over by well-trained whole-time men. Not only were laboratories for pathology, bacteriology and clinical microscopy provided, but also for chemistry, physics and animal experimentation, with a well-equipped machine shop to make new apparatus and surgical instruments. The men presiding over these scientific activities have been called from various universities; and, an internist, to work on borderline subjects between medicine and urology in both a clinical and experimental way, also devotes his entire time to the institute.

This close co-operation between scientific and clinical staffs has already proved of inestimable value, and the free discussion of the problems has been of much mutual help and inspiration.

All surgery has become so perfect in technical detail that advancement in the future will come from researches in the broader fields of chemistry, physiology and experimental medicine and surgery, but these can be very fruitful only when closely associated with the clinical work, and when the clinicians themselves become laboratory men and experimentalists. Such it has been our effort to provide for, with the belief that urology furnishes a most fertile field for research, and in the full expectation that it has a most brilliant future ahead of it.

WHAT WAS THE ENGLISH SWEATING SICKNESS OR SUDOR ANGLICUS OF THE FIFTEENTH AND SIXTEENTH CENTURIES?¹

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Contemporary writers differ about the exact date of the landing at Milford Haven of the Duke of Richmond in the year 1485. Presumably the date of August the first is correct, as this is the day mentioned in the *Historia Croydenensis*.² The invading army proceeded by way of Cardigan towards Shrewsbury, where it crossed the Severn; thence to Newport, Stafford and Lichfield, where it was encamped by August 18 on swampy, fenny land. Bosworth field is not far from Lichfield, and here was fought the battle which ended in the defeat and death of Richard III. Three weeks had elapsed between the landing and the battle, and on the march about 200 miles had been covered by Richmond's men. In view of the slow movements of the military forces of that day, caused by the weight of armaments, impedimenta and bad roads, the march was a very rapid one, involving more than usual hardships. During the passage from Havre to Milford Haven, which took seven days, much sickness developed among Richmond's mercenaries, and after the landing a large but unknown number of them had to be left behind along the line of march. Many of these died shortly after having fallen ill, and apparently the malady was rapidly transmitted to the inhabitants, spreading terror in all directions, for we know that Lord Stanley, temporizing, and peremptorily summoned by Richard, pleaded as an excuse the ravages of the new distemper. After his victory, King Henry VII in four days proceeded to London; and probably, according to the custom of the times, his army was disbanded. By September 21 Bacon³ reports a general prevalence of the deadly malady in London, where during five weeks "infinite persons," and according to Stow⁴ "a wonderful number," succumbed. By the end of the year the epidemic had spread with undiminished virulence all over England, sparing neither poor nor rich. Many were its victims among the clergy, gentry and nobility. When it appeared at Oxford, teachers and students fled. No exact data exist regarding the number of the dead, but it must have been very great. The medical profession was overwhelmed by the new disease and stood helpless in the face of the calamity.

Baker⁵ states that "many thousands died," and "no physick afforded any cure." The contemporary authors are silent about the part played by the medical men in this epidemic. Even the famous Linacre, founder of the College of Physicians, who in

his young days had witnessed the panic caused at Oxford at the first invasion of the disease, and who lived through two more of the epidemics, makes in his writings no mention whatever of it. This peculiar circumstance might be explained by the fact that the men who revised the study of the ancient medical writers—Linacre one among many—devoted more time and effort to diacritical research in the writings of Hippocrates and Galen than to the actual observation of maladies.⁶ The most learned ones among them were rather profound linguists than adroit physicians. Erasmus, a close and admiring friend of Linacre, did not fail to perceive this anomaly; nor did he hesitate to launch a shaft of sarcasm at the linguistic pedantry of the learned of his day. The famous passage on page 200 of his "*Laus stultitiae*" is generally accepted as applicable only to Linacre. "I have known a certain man of universal learning (polytechnotaton) of Greek, Latin, Mathematics, Philosophy, Medicine, and all the regal pomp of erudition, although past 60, to neglect everything during more than 20 years, so that he may freely torture and crucify his mind at digging in grammars; who has directly stated that he would consider himself fortunate if permitted to live long enough to be able to explain, without any doubt, in what manner the eight parts of human speech could be certainly distinguished, one from the other."

Whether with or without the aid of the profession, the common sense of the laity finally evolved a method of treatment which at least proved to be harmless and was generally accepted all over the kingdom. Its essence was the avoidance of all violent methods and remedies, abstention from food, scanty potations of mild beverages, and confinement in bed during 24 hours under light coverings. The fear of suppressing the perspiration suggested the rule that those attacked in the daytime should seek their beds with their clothes on; those that sickened during the night were not to rise; all avoiding exposure to the outer air of any part of the body except the face. By New Year's Day, 1586, the disease had vanished from England.

Before proceeding further it will be necessary to add some facts collected by the indefatigable Hecker that may have had an important bearing on the development of this pestilence. The first one is this: That since the year 1482 there had existed in France a murderous disease which is called by Mézeray⁷ "une

¹ Dr. I. F. C. Hecker: *Der Englische Schweiss*, Berlin, 1834.

² Joannes Tell: *Rerum Anglicarum Scriptores veteres*, Oxon., 1684.

³ Francis, Lord Verulam: *The Historia of the Raigne of King Henry the Seventh*.

⁴ John Stow: *The Annales of England*, etc., London, 1592.

⁵ Sir Richard Baker: *A chronicle of the Kings of England*, etc., London, 1665.

⁶ The later Greek authors, according to Hecker, ignored the existence of small-pox during four centuries, because there was no mention of the disease in the writings of Galen. Linacre might have found an excellent description of the sweating sickness in Aurelianus, a Roman physician of the fifth century, whose language, however, characterized by many romance elements, was considered corrupt; hence the author was ignored.

⁷ François Eudes de Mézeray: *Histoire de France*, 3 tomes, Paris, 1682, t. 2, p. 746.

dangereuse et mortelle maladie," which, "though not contagious, attacked indifferently great and small." It was a species of hot and frenetic fever, which suddenly inflamed the brain and scorched it with such cruel pains that some broke their heads by butting the walls; others jumped into wells, etc. The chroniclers all report that the year 1485 was preceded all over Europe by five excessively wet years with continuous rains and many inundations; the crops failed to mature in most places, and famine stalked through all Europe. The year 1486 was the sixth wet year in succession, and inundations of the Tiber, the Po, the Danube and the Rhine were recorded.

The composition of Richmond's army also deserves attention. Its bulk consisted of armed mercenaries originally licensed by Louis XI, free lances—that is, the scum of humanity—to join whom there flocked all that were given to crime and vagrancy. Mézeray says of them: "There were in Normandy alone some troops of free lances (*francs-archers*) belonging to those permitted by Louis XI, and who travelled the country; and being joined by many vagrants they ravaged all the land, so that the fear arose that the evil might be spread to adjoining provinces; but just then a good occasion presented itself to deliver France of these robbers, and he (Charles VII) gave him (Richmond) all these free lances and brigands of Normandy to the number of 3000."

It is easy to imagine what the hygienic conditions must have been in the midst of which lived this armed mob. The crowding and uncleanness on board the small vessels during the week elapsing between July 25 and August 1 must have been excessive, and must have served as hotbeds for the spreading of the disease.

Let us cast a glance now at the manner of life that obtained in the England of those days. In great contrast with present conditions, the state of untidiness of English dwellings was truly Scythian. Erasmus, who never was contradicted regarding the matter, writes: "The flooring of the houses is usually beaten clay; this is spread with rushes, which are rarely removed, additional layers being added to those already fouled, which sometimes remain undisturbed for the period of 20 years; this mixed with fishbones, vomit, and other filth, becomes saturated with human and canine urine." Undoubtedly there is in this description much exaggeration, but the universal use of rushes on the flooring of the houses of even the wealthy is a well attested fact. The prevalence of vermin among the poorer sort, as to-day in the near East, was an accepted condition, against which even the better situated struggled with uncertain success. As we know the magnitude and difficulty of the task of keeping present-day armies free from vermin, we shall have no difficulty in imagining conditions in 1485. To recapitulate, these factors have to be kept in mind: The importation of a febrile disease from France by an undisciplined army of freebooters, who had spent a week at sea closely confined and crowded into the unclean, small vessels of the period; the entrance of this infected army into England, exhausted by the murderous wars of the Roses, and impoverished and starved in consequence of a series of failures of crops, which had never matured during years of rainy and cold weather;

the dwellings, almost exclusively built of wood, or wood and bricks, small, crowded, filthy, and all more or less infested with lice, ticks and bedbugs. The prevailing cold weather was, of course, a powerful incentive to crowding and uncleanness. Here we have a combination of factors unsurpassed to serve as the hotbed for an epidemic.

Of the writers of the period who recorded the events of the malady, it might be said that all of them were laymen. From Linacre we have not a line written on the new disease. The descriptions of the symptoms of the disease and of the manner of its spreading are very scanty and unsatisfactory. They are also often contradictory; but this much can be gathered from them: That the onset was sudden; that the fever was excessive, initiated by a chill, accompanied by headache, anorexia, vomiting, backache and pain in the muscles and long bones; that it attacked all ages and conditions; killed in the first access of pyrexia not only those enfeebled by want or exposure but many of the better situated and seemingly strong, who indulged in perpetual gorging of almost exclusively animal and highly-spiced food, together with alcoholic excesses, the chief amusements of polite society. The consumption of beer by the populace was not diminished but rather stimulated by the general misery, and the habitual beverage of the well-to-do consisted of strong wines imported from Greece, such as Muscatel and Malmsey. Vegetables were not cultivated, so that Queen Catherine had to import soup-greens and lettuce from the continent.

At the acme of the fever coma supervened, which was soon followed by death, sometimes within two hours after the onset. All the authors lay stress on the circumstance that after the lapse of exactly 24 hours an excessively profuse and nauseatingly foul sweat broke out all over the body of the patient, after which there followed either a remarkably speedy recovery or a slow and protracted convalescence. A return of the fever was very frequent, and occurred once, twice or oftener, as many as 12 recurrences being mentioned. Few of the writers, however, lay stress on the phenomenon of recurrence, their attention being entirely dominated by the more obvious symptoms—the rheumatic pain, the headache, the burning fever, the coma and the ill-smelling profuse sweat. Most of them, Bacon among the rest, did not consider the disease epidemic (meant for contagious) like the plague, because many were attacked who had had no contact whatever with the sick. All writers accepted the theory that the malady was due to an atmospheric poison, precipitated from the perpetual pall of fog and rain. Remarkable is the unanimity of all the contemporary authors regarding the sudden and complete cessation of the disease.

The second invasion by the sweating sickness occurred in 1506, only seven years after the terrible destruction of life wrought in 1499 by the plague. In London alone there died 30,000 persons, and the King fled the country, retiring to Calais. On the whole, this epidemic was milder than the first.

The third epidemic appearance of the sweating sickness took place in the year 1517. It ravaged the country during six months, having spread to the frontiers of Scotland. Among the general conditions that might have favored its development,

the following may be mentioned: The end of the reign of Henry VII and the beginning of that of Henry VIII witnessed a remarkable development of England's industrial life. The conversion of much arable land into pasture caused a noteworthy migration of the farming population to towns and cities. Large numbers of Genoese, Lombard, French, German and Dutch tradesmen had settled in England. Under the stimulus of their skill, enterprise and industry, a flourishing trade established itself. Great prosperity but excessive crowding resulted. As the invasion of the towns by the starving country people could not be checked, much unemployment, poverty and squalor followed. All the towns were noted for their narrow and uncleanly streets, and a large proportion of the poorer inhabitants were housed in damp and incommensurable cellars. Contrary to the conditions of 1485 and 1505 the weather was not unusually rainy, and the crops were satisfactory. The opulent manner of eating and drinking of the industrial classes was stimulated by prosperity; a wellbeing from which the unemployed and vagrant poor were excluded—a condition essentially unchanged to this day. Bloody riots of the unemployed in London occurred in April and May, 1517, remembered under the name of the "Insurrection of evil May day." In July the sweating sickness broke out among the poor, and Goodwyn¹ says, "Of the common sort, they were numberless that perished by it." The wealthy, however, did not remain exempt. Ammonius, the King's secretary, having boasted to Thomas More of his immunity, due to simple habits, died two hours afterward. Of the court, there died Lords Grey and Clinton, besides a large number of attendant nobles and other persons of the household. The King fled to the country, frequently changing his abode, whereto he was followed by lugubrious news, reporting that in this town or that one-third or one-half of the population had died. The usual festivities of Michaelmas, even those of Christmas, were abandoned. Thomas More's family was not spared, his daughter, Margaret Roper, having fallen sick. She recovered, however. In one of his letters to Erasmus, her father's distress found expression in this sentence: "Almost all being stricken within a few days, most of my best and honored friends were taken away." The acme of the distemper was reached six weeks after its beginning. Oxford and Cambridge suffered great loss in the deaths of their best teachers. The Scotch and Irish were spared, but the malady extended to Calais, where only the English were affected, the French remaining untouched.

In 1528 the sweating sickness appeared for the fourth time in England. This epidemic became noteworthy for several reasons. First, it was more destructive than the preceding ones; secondly, it spread to Holland, Northern Germany and the Scandinavian countries. As to the meteorological conditions preceding and during the disease, all writers of the time agree that 1527 and 1528 were excessively wet and cold years, not only in England but over most of Northern Europe, so that Count Newenar, Canon of the See of Cologne, wrote as fol-

lows: "There were in that and during the preceding years so many storms, inundations, cold spells combined with perpetual humidity, that it seemed as though the climate of Great Britain had taken possession of Germany." In England there was incessant rain during November and December, 1527, and in January, 1528, resulting in extensive inundations which killed the winter crops. The spring sowing was scarcely finished when, in April and May, it rained continuously for eight weeks. Thick fogs covered the country in the pauses between the rains, and destroyed the last hope for a harvest. Such weather prevailed during a succession of years over most of Europe. The chronicler of the city of Erfurt reports that after an unusually mild winter-spring set in so early that on St. Matthew's day (February 24) everybody was wearing posies of wild violets. The rest of the spring and the summer brought an unending succession of rainstorms, causing widespread inundations and a total failure of the crops. The resulting famine was appalling, cattle and even the birds of the air dying in great numbers. Among the expedients resorted to during the calamity may be mentioned the following: When the season drew to its end parts of the green crops that had not rotted out were cut, and the ears of grain were parched in ovens to be eaten in the shape of porridge.

The "Great Dying" began in London during the last week of May, 1528, spreading thence all over the realm. The virulence of the malady was terrifying, most of the afflicted passing from wellbeing to death within five or six hours. Quarter sessions were suspended, and notwithstanding general protestation, St. John's day solemnities and feasting were suppressed. From among the courtiers, Sir William Compton and William Carew, both chamberlains to the King, died in quick succession; and when Sir Francis Poynes, the recently returned ambassador at the Court of Spain, succumbed, the King fled London and wandered about the country until he settled down in the solitudes of Tytynghar, surrounded by a chain of bonfires, kept up day and night. The combination of famine, of a depressing humidity, and the consequent crowding together of starving multitudes in filthy habitations, were the leading factors of this epidemic. There exists no reliable record of the mortality, but it must have been greater than in any of the preceding epidemics, as some of the writers use the term, "universal depopulation." The epidemic itself was dubbed by the people "The Great Dying." It is a strange fact that not one of the writers of the time noted the duration of this epidemic, and it is fair to assume that sporadic croppings up of minor foci and of scattered single cases dragged out the disease into the year 1529, so that the precise ending could not be determined.

In this year, with the arrival of the skipper Hermann Evers from London on July 25, the disease made its first appearance in Hamburg. Twelve of the ship's company died, some at sea, four after their arrival in Hamburg. The epidemic lasted 22 days and caused the death of 1100 of the inhabitants. The count is exact, because this was the attested number of coffins delivered by the joiners' guild. The distemper appeared in

¹ Francis Goodwyn (Bishop of Hereford): *Annals of England*, etc., London, 1675, p. 23.

² Hecker: *Foot-note*, p. 93.

quick succession at Lübeck, Zwickau, Stettin, Danzig, Augsburg, Strassburg, Köln, Frankfurt am M., Marburg, Göttingen and Hannover. The cropping out of the disease as to choice of locality was capricious, but this much is evident, that the further south it extended the milder and rarer it became. Amsterdam was stricken on September 27. From there the mischief spread over all of Holland and Belgium. Alkmaar and Waterland alone remained intact. At about the same time the sickness invaded Denmark where, in Copenhagen, on one day, September 29, 400 persons died. It also appeared in Norway and Sweden. Within three months of its first appearance in Scandinavia the epidemic ceased. The strange silence of contemporary English medical writers about the sweating sickness, which they had abundant opportunities to observe during the preceding epidemics, has been mentioned before. The learned doctors of the universities were under the scholastic spell of the ancients. Whatever did not occur in Hippocrates or Galen did not interest them; it was simply ignored. The number of these highly learned linguistic doctors was small, and not all of them practised. The great bulk of medical work was in the hands of licensed or unlicensed, mostly illiterate, ignorant surgeons and barbers. Medical writing was in Latin and inaccessible to the commonalty. The Catholic faith was still unshaken in England; nay, the King had entered the lists against Luther's heresy, thereby earning the title "Defensor Fidei," still attached to the English crown.

By the time the disease penetrated to Germany, however, the country had been in the throes of the great reformation full 12 years. Religious controversy of the most passionate character was in full blast, its main vehicle being innumerable sheets and broadsides printed in every town of note. Gradually other than religious questions of public interest were seized upon by the pamphleteers, who used this convenient medium to spread their opinions on politics, trade, education, national economy and what not, among an eager and awakened public. The new and murderous disease became naturally a subject of much controversy and of universal interest. Though most of them have disappeared, there is still extant a rich array of pamphlets and broadsides printed in Holland and Germany from the pens of medical men, humble and eminent, and also from a host of laymen of various character. There were even official publications, such as that of the great Council of Berne, whose purpose was to combat the universal terror and to give therapeutic directions of a mild and prudent nature. From these pamphlets we gain many valuable observations regarding the facts of the malady and of the curative measures employed against it.

As the valuable experiences gathered in England were unknown, the appearance of the epidemic found both profession and people of the Continent unprepared. The first pamphlets appeared in the Netherlands, written mostly by greedy and ignorant quacks. The fact that the febrile attack was usually terminated by a critical sweat led them to the conclusion that an artificial production of profuse sweating would favorably terminate the disease. Hence it was recommended that the

sick should be smothered in heavy featherbeds; that, all chinks and apertures of the bedroom being carefully stopped, a huge fire should be started in the chimney, and that heating drinks should be copiously administered. This procedure became known as the "Netherlands Regimen."

Soon, however, primarily through the efforts of a protestant English gentleman, Dr. Barr, who lived in Lübeck, and who was a learned man and a philanthropist, information about the English method of treatment filtered into public knowledge, and this led to the abandonment of the execrable and murderous "Dutch Regimen." Featherbeds were condemned and more rational, less active measures were adopted. Nevertheless, we see curious preoccupations persistently cropping up. One of them was that if the patient lapsed into sleep, he was irremediably lost. Evidently sleep and the deathly sopor of fatal coma were confounded. Hence heroic, but nevertheless ridiculous and useless efforts were made to prevent sleep. In the otherwise useful broadsheet of an unknown author printed at Wittenberg—the text, written in the vigorous and pithy vernacular of the sixteenth century, is well worth reading—we are told: "Item.—Two men should have charge of the patient, to prevent his uncovering himself and his falling asleep. Item.—The men should watch and prevent sleep. Should, they not beware, the patient fall asleep, then he will lose his senses and will go mad. To ward off sleep apply rosewater to the tender parts of eyes and ears with a sponge or cloth, or better still put strong wine or sharp vinegar into his nose, talking to him all the while that he may stay awake. Item.—As to those who lie naked, should they refuse to keep still, then sew them up in the sheets with needle and thread and sew the sheets to the mattress, so that no air should get to them. Then spread the blanket."

Urtius Damianus, a popular practitioner of Ghent, went much further, in recommending that, the ordinary means for preventing sleep being ineffectual, single hairs should be plucked off the patient's head or beard, his members be forcibly and painfully constricted, and vinegar be instilled into the conjunctival sac. Most of the authors, however, advised against the use of sharp measures, such as vomitives, purges, venesection and the heating Dutch treatment, preferring what we would call nowadays the expectant method.

From this abundance of sources it is not difficult to construct a fairly precise clinical picture of the sweating sickness. Singly taken, the authors are not free from the ignorance of their age. One of them "saves himself all trouble by stating 'The signs of the disease are manifest; those omitted might be reproduced from the reader's imagination.'" But taken altogether, the testimony of these continental authors represents a great advance over the paucity of the English.

"Hecker: pp. 129-130.

"Schiller. Joachimi ab Herderen, physici: De peste Britannica, etc., Basilee, 1531.

The unanimous assertion that the duration of the fever is precisely 24 hours need not be taken literally, for several of the writers admit variations. Thus we see Schiller saying "Habet inconstantes notas morbus," and Damian, "Diversus diversimode adoritur." I lay stress on this reflection for a reason that will become apparent later on.

The onset began with a chill, followed by very high fever, the patient frequently lapsing into coma. The chill was inaugurated with formication of the hands and feet, painful sensations under the fingernails, and deep prostration. Intense headache and backache, anorexia and vomiting, "broken-bone pains" of the limbs, later on delirium and coma, were the ordinary features. Dyspnoea, with cyanosis, set in with unconsciousness and generally led to death. The pulse was throughout very high and gradually became weaker; often heart-failure ended the process at the acme of the fever. After the lapse of 24 hours, the surface of the body became bathed in a most profuse and fetid perspiration. The action of the bowels and of the kidneys also showed variations. Sometimes it remained normal, then again it was suppressed. Exanthems: A vesicular eruption like our prickly heat (sudamina) is occasionally mentioned. Fatal cases, on the other hand, showed "bullæ, petechiæ, rhonchæ et pustulæ." The fear of suppressing perspiration was universal, a phantom that has survived until this day. Relapses were frequent, if not the universal rule, but each relapse was looked upon as a new invasion of the disease, the embodiment of which was conceived to reside in the single febrile attack. John Kaye mentions a case in which 12 were noted. Of autopsies there is no record. In England, as well as on the Continent, we meet with the assertion that the disease attacked mostly persons of middle age, and that children and old people were spared. Not one of the observers lays any stress upon the obvious fact that the ravages of the disease were most prominent among those enfeebled by want and privation, who naturally were the most subject also to excessive crowding in filthy dwellings.

The sweating sickness appeared in England for the fifth and last time at Shrewsbury on April 15, 1551. From here the malady spread again over the realm, diminishing gradually until the end of September, when it ceased. The morbidity was unexampled, the mortality appalling. Within a few days 960 of the inhabitants had died. City dwellers fled to the country, farmers from the country to the town. Many escaped to Scotland, Ireland, and to the Continent; daily labor ceased and the tolling of mortuary bells sounded uninterruptedly day and night. The loss of life was very great. No layer of society was spared. In this instance, again the fact is restated by John Kaye," that the disease followed Englishmen wherever they went, not affecting, however, the natives. "And it so followed the Englishmen, that such merchants of England, as were in Flaunders and Spaine, and other countries beyond the sea were visited therewithall, and none other nation injected therewith." (Page 30.) This asser-

tion is supplemented by another, according to which foreigners living in England remained immune. During this epidemic a curious phenomenon previously observed during the second invasion reappeared in England. Moulds of various colors, mainly red, but also white, yellow, ashy and black, became established on roofs, on clothing in use, even on stomachers and veils actually worn by women. Clothes kept in presses were spoiled, and utensils, articles of food fresh and preserved, were tainted by it. Frequently rain fell that was fringed with this mould, giving color to legends of rains of blood."

This last invasion of the sweating sickness is notable for the fact, also, that it produced the first English medical publication dealing with it. The author was no less a man than John Kaye, the Caius of Gonville Hall, later Gonville College, now known as Caius College. At Henry VIII's request he lectured to the London Surgeons on anatomy. He became the physician of Edward VI, and was retained in this capacity by Queens Mary and Elizabeth. He became Linacre's successor in the presidential chair of the College of Physicians, and endowed two annual public autopsies, the first ones practised in England. He witnessed the epidemic of 1551, both at Shrewsbury and in London. His pamphlet dealing with it appeared in 1552. It is written in the forcible vernacular of the day, frankly condemning the coarse feeding and drunken habits of his countrymen; it eschews all learned verbiage, reserving erudition for the Latin edition of the opuscle. Like all his contemporaries, he attributed the malady to the effect of poisoned air. As a prophylactic, he recommends the use of cleansing bonfires, and supports the advice by the statement that cooks and blacksmiths showed a remarkable immunity. His treatment consisted of mild methods well established in England during the preceding epidemics. He deprecated all drastics, and condemned the forcing of perspiration, and the cruelties we read about in Damian. He was a versatile author, as attested by writings on subjects of natural history, which were dedicated to Conrad Gesner (among these is a volume "De canibus britannicis"), and by essays on historical and antiquarian matters. He died in 1573, ordering his epitaph to be: "Fui Cajus."

It is about 20 years ago that I came across and read Hecker's remarkable monograph on the sweating sickness. Intense interest was heightened by the puzzling uncertainty regarding the identity of this disease, which was dispelled only by acquaintance with the characteristics of the recurrent or relapsing fevers of modern times. By re-reading Hecker several times, and by employing the method of exclusion, I finally came to the conclusion that the sweating sickness observed in England and on the Continent in the fifteenth and sixteenth centuries must have been one of the virulent forms of relapsing fever, such as is rarely observed nowadays. The essential points are congruent, common factors being an infection carried by living parasites to human beings crowded together in filthy abodes, and as a predisposing

"Caius, John: A booke or Councell against the Disease commonly called the Sweate or Sweatynge Sickness, London, 1522.

"The chroniclers called this phenomenon "Lepra vestium."

element an enfeebled state of health caused by hunger, exposure and moral depression.

Thanks to Obermeyer we know that the causal parasite is the *spirochæta febris recurrentis*, which reaches the blood by various accidental forms of inoculation. The carriers of the disease are mainly head and body lice, ticks and possibly also the bedbug. In Europe it is to-day, as it must have been in England in the fifteenth and sixteenth centuries, a disease of the lousy. Nicholle has shown, in 1912, that lice hatched from eggs of infected lice are also infected. The same thing has been established regarding the eggs of the tick. Africa is the home of tick fever, while the pedicular forms are endemic in India, Central Asia and Eastern Europe. There is doubt as to the exact modes of inoculation. The entrance of the *spirochæta* was first assumed to be marked by the bite of the insect, but this is now questioned. As the *spirochæta* and its spores are mainly found in the intestinal tract of the insect, inoculation by the bite is unlikely. Experiments have demonstrated that the point was well taken; but if the debris of the crushed insect is rubbed into a fresh scratch, infection invariably follows. The capriciousness of the spread of the disease, formerly so unaccountable and puzzling, is readily explained by the capricious vicissitudes to which are subject the rise and fall of pedicular proliferation. The conditions parallel the puzzles presented by the transmission of malarial and yellow fevers, typhus, the plague, etc., by which older medical practitioners were sorely mystified.

In comparing the natural history of recurrent fever as observed in our day with the composite picture yielded by the writers who saw the sweating sickness of the fifteenth and sixteenth centuries, we find a general similarity of characteristics. But there are discrepancies which deserve attention. One is the statement that invariably 24 hours after the onset the fever was resolved by profuse critical sweating. Modern observers have found, on the other hand, that the duration of the febrile attack between initial chill and crisis is from 3 to 10 days. We have quoted two writers, Schiller and Damian, who explicitly mention the great diversity and inconstancy of the features of the disease. Considerable variations in duration and virulence are noted even to-day in various epidemics, and but for the sheet anchor of the blood test some of the more atypical might even now not be easily identified. The fact that the writers have looked upon the individual febrile attack with its saliences as the sum total of the disease, failing to recognize the essential importance of the tendency to recurrence, is not to be wondered at. The validity of the statements referring to the sudden cessation of the epidemics at the end of summer cannot well be questioned. All, with the exception of the first one, began in April or May and ended by October; therefore, they must be declared to have been summer weather

epidemics—summer weather, to be sure, that was very damp and cool. It is interesting to compare this fact with the predilection of typhus fever, another disease of lousiness, for the winter months. The explanation may be found perhaps in the consideration that the inclemencies of the summer weather and the want prevailing during these epidemics had produced conditions almost identical with those that determine the hibernal eruptions of spotted fever. More difficult to explain are the assertions regarding the selective tendency of the sweating sickness, which is indicated in the statement that it followed Englishmen abroad, sparing the natives; foreigners living in England remaining also immune during the worst times of general sickness. The one great exception to this rule is found in the murderous sweep made by the malady through Northern Europe. Nevertheless, the repeated mention of this peculiarity must induce the reflection that the level of the personal habits of the generality of Englishmen of those days must have been below that of the continentals, a surmise of not much significance at a time of universal hygienic ignorance and neglect. As to the nature of the sweat exuded at the crisis and its excessive fetidity, contemporary statements are also unequivocal and unanimous. The sweat of rheumatic fever, having a peculiarly disagreeable acidity of odor, might be compared with it, but nobody would think of ascribing to this characteristic such stress as is done by these authors. The universal terror, the continuous spreading of rumors and the accounts of quick death, sweeping away masses of seemingly healthy people within a few hours, fear heightened by ignorance and superstition, must undoubtedly have created a general state of mind prone to overstatement and wild exaggeration. In times of stress and danger caused by war and pestilence nothing appeals more to the vulgar mind, ignorant or learned, than vehement assertion of the monstrous and ordinarily unthinkable; and nothing is more readily and passionately accepted. Each of the modern wars, the present one included, has furnished thousands of illustrations of this tendency. Once pronounced and vociferously repeated, such statements without adequate proof, become matters of universal belief and dogma.

SYNONYMS.

Febris sudatoria; *morbus Anglicus*; *morbus sudatorius*; *pestis Brittannica*.

The Sweat; Sweating Sickness.

La Svette.

De Schwetende Sicke (Platt).

Englischer Schweiss; Schweissucht; Schweiss-Krankheit; Hungerpest.

Schwitzende Seuche.

Der Engelske Sved.

Engelske Svetten.

Ἰδρυνόσος; ἰδρωπικός.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXVII is now in progress. The subscription price is \$2.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, \$2.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

NOTES ON NEW BOOKS.

Pellagra: An American Problem. By GEORGE M. NILES, M.D., Atlanta, Ga. Second edition. Illustrated. \$3.00. (Philadelphia and London: W. B. Saunders Company, 1916.)

The appearance of the second edition of this book is timely, in view of the large additions to our knowledge of pellagra during the past four years. The author approves Lombroso's dictum "In pellagra we are dealing with an intoxication produced by poisons developed in spoiled corn through the action of certain micro-organisms in themselves harmless to men," but would add to the words "spoiled corn" "spoiled carbohydrates."

The chapter entitled "General Considerations, Historic and Otherwise" presents an excellent résumé of the history of the disease since its first discovery. In the account of "Pellagra in the United States" we notice that he fails to mention a case reported by Babcock in the *American Journal of Insanity*, July, 1912, with the facsimile of the notes on a patient admitted to the Columbia State Hospital, February 14, 1834. This seems to have been an undoubted case. The other chapters of most interest relate to the etiology and treatment of the disease. The chapter giving details of experimental work is inconclusive and unsatisfactory. The book as a whole presents an excellent account of our present knowledge of pellagra.

Nervous Children: Prevention and Management. By BEVERLEY R. TUCKER, M.D., Professor of Neurology and Psychiatry, Medical College of Virginia. \$1.25. (Boston: Richard G. Badger, 1916.)

This book of 147 pages is "to be read with equal interest," according to the hope of the author, "by the physician, the school teacher, the mother and the intelligent nurse." It is clearly written and attractively printed. It presents little that is new, but portions of it seem well adapted to the instruction of well-intentioned parents.

Diseases of the Arteries Including Angina Pectoris. By SIR CLIFFORD ALLBUTT, K. C. B., M. A., M.D., F.R.C.P., F.R.S., Hon. M.D., LL.D., D.Sc., etc., Regius Professor of Physic in the University of Cambridge, Fellow of Gonville and Caius College, Hon. Fellow New York Acad. Med., etc. In two volumes. \$9.00. (London: Macmillan Company, Limited, St. Martin's Street, 1915.)

To him who has once ventured into the dark in its pursuit, arterio-sclerosis is the will-o'-the-wisp of medicine, appearing now here and now there with seeming lawlessness, its explanation in one case grasped, yet in the next seeming more far away than ever. Elusive, tantalizing, its pursuit exercises an irresistible fascination over all who have allowed themselves to be drawn into it. These are a goodly company, with many of the best minds that have studied medical problems from the viewpoint of pathologist or physiologist or clinician. Among them Sir Clifford Allbutt, through a long life, has again and again turned to this quest, now in the laboratory, now at the bedside, and through it all, in his library, has been amassing a tremendous knowledge of the phenomena of arterial disease seen by other eyes than his own, and of the views, outworn and current, advanced by other workers in explanation of their causation. Now, rich beyond the usual lot of men in years, in knowledge and in experience, he has brought together in two volumes the results of the favorite labors of his life.

These volumes contain such a mass of facts and so painstaking and compendious a recital of argument on all phases of these oft-debated subjects that it is impossible to review them in detail. Beginning with an historical introduction, the subject is approached first from the standpoint of the physics of the circula-

tion, in a very complete chapter, followed by an interesting discussion of the viscosity of the blood. Then arterio-sclerosis is considered from the standpoint of its many possible and probable causes in a chapter of 154 pages. The author closes with the following paragraph:

"In revising this chapter on the Causes of Arterio-sclerosis I sympathise with a reviewer who, after reading a certain dissertation on another disease, exclaimed, 'We would ask what the conditions are which do not bring on this malady!' And every failing element is both cause and effect."

Nevertheless, he does lead the reader to a viewpoint from which the otherwise hopeless tangle of fact and theory which he presents may be seen to take on definite form and order. This viewpoint envisages arterio-sclerosis as an omnibus name crudely signifying the anatomical result of several morbid processes, not as a disease, a definite etiological entity. For him arterio-sclerosis is of two main types. One associated with, and caused by, high arterial pressure he names "hyperpietic"; the other, a degenerative lesion seen typically in the aged, dependent upon various infectious, toxic and other unknown factors, he distinguishes as "decrecent" arterio-sclerosis. This view, in the main, he has long preached. The term "decrecent" he has substituted for the word "involutionary," formerly used by him in the same sense, but which he considers less exactly descriptive. This viewpoint is coming to be very generally held by students of the subject, and the reviewer is in entire sympathy with it. Faber, in his recent monograph, endeavors to bring a further unity of the two types in a mechanical conception of disproportion between internal strain and strength of the vessel-wall. It is to be hoped that physicians generally may acquire some such point of view and give the diagnosis of arterio-sclerosis, as the designation of a disease embracing everything from syphilis of the aorta to chronic Bright's disease, a much-needed rest. The reviewer doubts, however, whether the rather pedantic terms "hyperpietic" and "decrecent" will do much toward popularizing the underlying ideas.

There follow in the first volume quite elaborate presentations of the relation of arterio-sclerosis to disease of the kidneys, of the symptoms and the morbid anatomy of arterio-sclerosis. The second volume continues with cardio-sclerosis and the effects of arterio-sclerosis and hypertension upon the heart, then a chapter upon diagnosis and prognosis which is curiously brief when contrasted with what has gone before, and is not particularly authoritative. The author feels unable to formulate any principles for the very important practical application of prognosis in life insurance. The chapter on treatment is full and contains much sane and valuable advice.

In Part Two he deals with aortitis and angina pectoris in the same complete and painstaking way. Chapter Six is a very valuable summary of all of the hypotheses that have been advanced for the explanation of the anginal paroxysm, covering 140 pages. His own belief, held for many years, that angina pectoris is fundamentally dependent upon disease of the wall of the ascending aorta, is only confirmed by his final review of the evidence. On page 422 of Volume Two he says:

"I have failed to discover a case of unmistakable angina in which, whatever the disease of the coronary arteries, the aorta, on careful examination, was demonstrated histologically to be inwardly and outwardly sound."

Whatever the final explanation of the whole mechanism of angina pectoris, Allbutt's theory has certainly received considerable confirmation from recent studies of syphilis of the aorta.

The concluding chapters on diagnosis, prognosis and treatment are good. The reviewer would call attention to a small detail to emphasize a fact not widely known, and evidently not appreciated

by the author. He states on page 534 that nitroglycerin by the mouth acts in about 10 minutes. This is true if it be swallowed. Do not, therefore, conclude that nitroglycerin acts too slowly to relieve an anginal paroxysm. Nitroglycerin should never be swallowed, but should be held in the mouth until absorbed, which requires somewhere between 45 seconds and a minute and a half, at the end of which time its systemic effects can almost invariably be detected.

A reviewer bent on hostile criticism might hold that the book should have been named "An Autobiographic Sketch of the Diseases of the Arteries." Those of us who know Sir Clifford Allbutt and his work; who appreciate his early recognition of syphilis of the vascular system, well in advance of its more complete description by the Kiel pathologist, and far in advance of contemporary medical opinion; who recognize the great weight of his authority in popularizing the use of instruments for measuring blood pressure, and of more exact physiological concepts in circulatory disease; who find his views on arterio-sclerosis and angina pectoris receiving more confirmation with the years, cannot but value very highly his own account of his researches and of the development of these views in his own mind. As a reference-book for the ready location of a fact or theory, the book has the serious defects of its author's well-known style. Those of us who do not agree with Sir Clifford that the ideals of scientific presentation and of artistic portrayal in literature are identical, cannot but regret that the storehouse of his erudition was not made more readily accessible to English-speaking workers in this field of which he is a master; but all of us who regard him with admiration and affection must admit his right to open that storehouse to us on his own terms and must express our debt of gratitude for his generosity with its contents.

THEODORE C. JANEWAY.

Local and Regional Anæsthesia. By CARROLL W. ALLEN, M. D. \$6.00. (Philadelphia: W. B. Saunders Company, 1914.)

This volume of 600 pages is the result of 20 years of earnest and laborious work on local and regional anæsthesia. The introduction is written by Prof. Rudolph Matas, to whom the volume is dedicated.

In the opening chapter the author gives a brief but interesting history of the development of local anæsthesia. Succeeding chapters deal with the sensations, especially pain, and contain a full discussion of the theories of pain. Under "Osmosis and Diffusion" the author points out the importance of using solutions of proper tonicity, in order that a minimal amount of pain may be produced and the best conditions for healing may be obtained. He gives a complete list of all the local anæsthetics known, and discusses fully their chemistry, toxicity and effect upon tissues (local), the duration of anæsthesia, etc. He concludes that novocaine is "at the present time the most commendable of local anæsthetics, and combined with adrenaline its value is greatly enhanced." The principles underlying the technic of administration are dealt with in proper detail.

The greater portion of the book is devoted to topographical anæsthesia. There are numerous diagrams, charts, and photographs representing anatomical dissections of various parts of the body, for the purpose of demonstrating the proper points and lines for cutaneous and deep infiltration.

Great care has been exercised in determining these various areas, and no portion of the body has been neglected.

The book is an exhaustive treatise on this subject of local and regional anæsthesia, but owing to its great volume and detail will be of value chiefly as a reference book, and to this end it should serve a great need. The hope of its author, however, will not be fulfilled, unless it is instrumental in diminishing the indications for general anæsthesia.

C. H. W.

The Alimentary Tract: A Radiographic Study. By ALFRED E. BARCLAY, M. A., M. D. Cloth, \$4.00. (New York: Macmillan Company, 1915.)

The first edition of Barclay's book on the radioscopy study of the gastro-intestinal tract was received with so much favor that a second edition became necessary within a year's time. In the present volume the author, besides making many additions to the subject matter considered in the first printing, has added some new chapters of very pertinent interest, notably one upon the etiology of gastric and duodenal ulcer and another upon various questions involved in the physiology and pathology of the large bowel. The conclusions are based entirely upon fluoroscopic studies, and this is of fundamental importance, because it calls attention to the fact that in the study of gastro-intestinal pathology, where as a rule function is so much more important than form, far better conclusions as to the underlying conditions may be obtained from the more plastic radioscopy than from the less plastic radiography, unless in the latter instance the case be studied cinematographically. That the study of the plates is so much more widely employed than the use of the screen in the digestive field is unfortunate, but it has been brought about by many factors, chief among which are the fear of the screen on the part of many operators and the far greater difficulties of technique. On the other hand, given an absolutely satisfactory apparatus and proper training in interpretation of the screen shadow, that the results obtained by fluoroscopy are more satisfactory seems to us to be beyond peradventure. The fact that we can study the patient in upright and in prone positions and that we can note the effect of respiratory movements and massage seem to us sufficient reasons for making this the method of election; and Barclay's extremely valuable contributions to gastro-intestinal pathology, based entirely upon fluoroscopic studies, accentuates this point of view.

The early pages of the book are devoted to discussions of technique, protection and the most satisfactory routine methods to be employed. Next, we find chapters on the œsophagus, the normal and pathological stomach, gastric ulcer, hour-glass stomach, gastric carcinoma and various other pathological gastric conditions, including a very interesting chapter upon the etiology of gastric and duodenal ulcer. Following these are chapters upon the small and large intestine in health and disease, the latter part of the book being devoted to an epitome of the cases considered and a very complete bibliography. Not the least interesting features of the book are the author's philosophical remarks, based upon these fluoroscopic studies, regarding various tendencies of the day in gastro-intestinal pathology and therapy. For example, "What is one man's food is another man's poison" is an old saying that expresses the fact that this complex nervous mechanism controlling the digestive tract is not standardized; that each individual is a separate creation, each bearing outward resemblance of a standard article. Even the gross appearances of a normal stomach vary in such a way that it is only a study of a large number that will give a true conception of the variations that are possible within the limits of the normal." Again, "If we could accept the universal 24-hour standard, the difficulties of writing on this subject would be comparatively slight, and dogmatism could be indulged; but since each case must be treated as an individual, the evidence deduced from watching the passage of a standard meal must be most carefully balanced with the clinical picture, before deductions are made." And finally, apropos of the much discussed colonic resection for intestinal auto-intoxication, "The fact that certain wholesale removals are successful (and this undoubtedly is true in a small percentage of cases) is no proof that they were necessary, but rather that somewhere in this large mass lay the cause of trouble"; and, "One is astonished, not so much at the brilliancy of the surgery displayed, as at the tolerance of the human body."

In each problem presented Barclay makes his attack from the physiological or functional, as well as from the anatomical or morphological, point of view; and this adds immensely to the value of his subsequent conclusions. We feel that this book affords the best presentation of the brief in favor of fluoroscopy in the diagnosis of gastro-intestinal diseases, and we can recommend it heartily not only to the special students in this field, but to every one interested in digestive pathology. F. H. B.

X-Rays: How to Produce and Interpret Them. By HAROLD MOWAT, M. D. (Edin.). Cloth, \$3.00. (London: Oxford University Press, 1915.)

The author has described in a clear and concise way the principles pertaining to the physics of x-rays, and especially the different sources of current capable of exciting the x-ray tube.

The chapter on the technique of examination and development of x-ray negatives is well worthy of mention, and should be very helpful to the beginner in roentgenology.

The remaining half of the book is devoted to interpretations of the plates and findings with the fluoroscopic method of examination. It takes up the question of the different changes seen on the plate and describes those that are most typical; but the text is far too brief and good roentgenograms for comparison are lacking.

On the whole, the book would only be suitable for a beginner or to one who does not expect to devote his entire time to the study of roentgenology. C. A. W.

A Text-Book upon the Pathogenic Bacteria and Protozoa. By JOSEPH MCFARLAND, M. D., Sc. D. \$4.00. (Philadelphia: W. B. Saunders Company, 1916.)

The fact that McFarland's text-book on bacteriology has passed through seven editions since its first appearance in 1896 is indisputable evidence of the esteem in which it is held by physicians and medical students. The present eighth edition comes to us in a volume of some 800 pages embodying the subject matter of bacteriology and protozoology in its widest sense. Not much need be said here that has not already been said of previous editions, since, while considerably altered in arrangement and somewhat changed in text, the book does not present any very noticeable alteration in its general treatment of the subject. Just as in earlier editions, the place of Koch in bacteriology is incorrectly represented. A reading of the historical chapter gives one the impression that the contributions of Koch were more or less logical amplifications and extensions of earlier investigation. We know, both from the effect of Koch's work on the development of the science of bacteriology, as clearly seen in the literature of the subject, and from the evidence of Koch's own contemporaries, many of whom are still living and active, that his work was revolutionary, and that the methods devised by him raised the science of bacteriology to a new plane from which its modern development began. The book is also full of mistakes. Thus, on page 458, one finds the statement that the pneumobacillus of Friedländer "may belong to the same group in which we find *Bacillus aerogenes capsulatus*." Manifestly, this statement can only be correct if we substitute the name *B. lactis aerogenes* for *B. aerogenes capsulatus*. On page 589 we are informed that the typhoid bacillus "finds abundant opportunity for growth and development, etc., and can be found in water, soiled clothing, dust, sewage, milk, etc., contaminated directly or indirectly with the intestinal discharge of diseased persons." References to investigations which substantiate this assertion are lacking, and without such references the statement may properly be challenged. On page 616 the statement is made that *B. coli* "may also be identical with *B. lactis aerogenes*," about which one may express reasonable doubt; and on page 625 the hog-cholera bacillus (*B. suispestifer* of Salmon and Smith) is described as fermenting lactose, which it does not do. Finally, on page 732, in

the chapter on Actinomycosis, no adequate reference is made to Wright's work, altogether the most important done for some years in this field, although four of the seven illustrations are taken directly from Wright's paper.

McFarland's text-book, as we see it, contains a vast amount of valuable information. It is still in need of thorough revision, however, in the course of which the author should apply the pruning knife liberally, cut out the many misstatements and generally bring the book up to the standard set by our other text-books of bacteriology and protozoology in this country.

Circulation in Health and Disease. By CARL J. WIGGERS, M. D. (Philadelphia: Lea & Febiger, 1915.)

It is proper that at definite intervals in the large book that records the development of a scientific subject there should be a summarizing chapter, in which a critical opinion should be expressed concerning the preceding work. Cardiac physiology, and as a result cardiac pathology, have made most wonderful advances in the past decade. This is well appreciated in considering our present knowledge of the arrhythmias and comparing it with that of 10 years ago, when the electro-cardiograph first came into general use. But such rapid strides are dangerous; they must be controlled carefully and dispassionately.

In his recent book on the Modern Aspects of the Circulation in Health and Disease, Dr. Carl J. Wiggers, in 350 pages, reviews an abundant literature well chosen and collected at each chapter's end, and colors his conclusions with the rich experience obtained in the physiological laboratory. The treatise is divided into three sections: Physiology of the Circulation, Graphic Methods for the Clinician, and Diseases of the Circulation. The last section briefly outlines the physiology of the diseases of the circulation, following the method of Krehl who is frequently quoted. The first two sections are especially to be commended, and will be read with interest by all cardiac investigators. The book is technical and perhaps the conclusions are somewhat dogmatic, but the suggestions and outlines for new work are abundant, and show clearly the careful consideration of a thoroughly trained laboratory worker. The criticism of the mechanics of the different "instruments of precision" is most instructive, and emphasizes the dangers of regarding laboratory information as necessarily conclusive. The book will hardly be suitable for daily use by the general practitioner, but is essential for the library of the "whole time" student and teacher. E. W. B.

The Book of the Fly: a Nature Study of the House-Fly and Its Kin; the Fly Plague and a Cure. By G. HURLSTONE HARDY. 80 cents. (New York: Rebman Company.)

This book gives in a popular way a few points on the identification of life histories of house-flies and some of the commoner species of outdoor flies. There is a short chapter on a family of flies which may go through part of their life cycle within the bodies of animals and occasionally of man. The subject of the dissemination of disease by flies is briefly touched upon, and new methods of conducting an effective warfare against them are suggested. An appendix gives a minute description of the structure of the fly and a list of 60 families with their distinguishing characteristics. The book is written for the general public rather than for the medical profession. M. C.

The Gold-headed Cane. By WILLIAM MACMICHAEL, M. D. With an Introduction by SIR WILLIAM OSLER, B. A., M. D., F. R. S., and a Preface by FRANCIS R. PACKARD, M. D. (New York: Paul Hoeber, 1915.)

American physicians are to be congratulated on the opportunity to secure at a small price this admirable reprint of one of the Classics of Medical History.

Perhaps no other single volume presents so attractive a picture of the clinical traditions of the great English physicians as this little volume published first anonymously by MacMichael in 1827, and in an enlarged second edition in 1828.

It is this second edition which has been so beautifully reproduced with all the original cuts. Its value is further enhanced by an introduction by Sir William Osler and a preface by Francis Packard, who gives us an excellent sketch of the life of the author. The publisher, Hoeber of New York, deserves the thanks and encouragement of the profession.

Nurses' Handbook of Drugs and Solutions. By JULIA C. STIMSON, R. N. \$1.00. (Boston: Whitcomb & Barrows, 1915.)

This Nurses' Handbook of Drugs and Solutions is essentially what the title implies. The preface intimates that it is also intended as a text-book in training-schools for nurses; but for this purpose it is too brief and would be wholly inadequate, on account of the lack of detailed information which it is essential for a nurse to know in order that she may work intelligently.

As a handbook, however, it should serve a very useful purpose. It is conveniently small, clearly printed, and deals with all of the more important drugs. The chapter on Weights, Drugs and Solutions is clearly and briefly written, and should prove valuable for reference. S.

A Guide to Gynecology in General Practice. By COMYNS BERELEY, M. A., M. D., etc., and VICTOR BONNEY, M. S., M. D., etc. Cloth, \$6.50. (New York: Oxford University Press, American Branch.)

The authors of this work are already known to the American profession through the publication in this country five years ago of their Text-Book of Gynecological Surgery, which was devoted wholly to the operative side of gynecology. The present treatise omits all details of operative technique. It is confined almost entirely to the medical side of this specialty, embracing in elaborate detail both general and special gynecological diagnosis, as well as non-surgical therapeutic measures. In other words, in America, it would be called a *medical gynecology*.

The subject matter is presented in five parts. The first of these describes the methods employed in making a gynecological examination. The second undertakes to instruct the student in the proper significance of gynecological symptoms. The third is addressed in a similar way to the interpretation of the physical signs encountered in the various pelvic disorders in women. The fourth has to do with treatment, and is accorded one-fourth of the entire text, detailed advice being given in all conditions amenable to non-surgical therapy. Finally, in part five, the medico-legal aspect of gynecology is presented in a most practical and readable form.

The index is unusually complete and is made especially attractive through the liberal use of bold-faced type for the sub-heads. This splendid index, together with an elaborate system of cross-references profusely scattered throughout the text, render immediately accessible any desired subject. The illustrations are of mediocre quality, but the publisher's work has been well done.

The book may be safely recommended, both to student and practitioner, as being a safe and helpful guide in this field.

E. H. R.

Practical Cystoscopy and the Diagnosis of Surgical Diseases of the Kidneys and Urinary Bladder. By PAUL M. PILCHER, A. M., M. D. Second edition. Cloth, \$6.00. (Philadelphia and London: W. B. Saunders Company, 1915.)

During the four years that have elapsed since the first appearance of this book urological studies have been prosecuted with extraordinary intensiveness. How fruitful this labor has been, is made strikingly evident by a comparison of the two editions.

The original logical arrangement of subject-matter has been retained, but with important revisions, amplifications and additions. Thus, an entire new section has been devoted to pyelography, appended to which is a series of illustrative radiograms contributed by Dr. Wm. F. Braasch, of the Mayo clinic. It is unfortunate that the value of thorium nitrate, recently discovered by Dr. J. E. Burns of The Johns Hopkins Hospital urological staff, and recommended as an ideal substance for pyelography, was not sufficiently well established at the time of the publication to be included in this section. It will undoubtedly replace all other substances used for this purpose. The chapters on disease of the prostate and on functional activity of the kidneys have been entirely rewritten so as to incorporate the more recent advances. Notable additions are to be found, too, in the section dealing with the therapeutic use of the cystoscope, special attention having been properly given to the use of the high frequency current in bladder conditions.

The book can be recommended, alike to specialist and practitioner, as a splendid presentation of the entire subject of cystoscopy. E. H. R.

An Introduction to Bacteriology for Nurses. By HARRY W. CAREY, A. B., M. D. (Philadelphia: F. A. Davis Company, Publishers, 1915.)

In this little book of 133 pages the author succeeds admirably in his avowed purpose of presenting clearly and in simple language the portion of the subject essential for the nurse to know.

It is based upon the lecture notes of the author after an experience of eight years in the teaching of nurses and may be highly recommended. T. P. L.

Materia Medica for Nurses. By A. S. BLUMGARTEN, M. D. (New York: The Macmillan Company, 1914.)

Blumgarten's *Materia Medica* does not seem especially suitable as a text-book in training-schools for nurses. The information contained in the book could have been very much condensed, thus avoiding repetition and making the book a more convenient size.

The language used is clear and simple and the definitions are well-worded. The classification of drugs is also good; but there is a good deal of repetition.

Information concerning the anatomy and physiology of the various organs of the body could hardly be considered as of great value in a text-book on *materia medica*.

The chapter on solutions is somewhat complicated and its usefulness would seem to depend entirely on the memorizing of arbitrary rules. As a reference book the work might be of use to advantage. M. S.

Collected Papers of the Mayo Clinic, Rochester, Minn. Vol. VI. 1914. Edited by M. H. MELLISH. \$5.50 net. (Philadelphia: W. B. Saunders Company, 1915.)

The papers are divided into six general parts: (a) Alimentary Canal (26), (b) Urinogenital Organs (13), (c) Ductless Glands (15), (d) Head, Trunk and Extremities (11), (e) Technic (8), (f) General Papers (5)—in all 78 papers by 28 authors.

In the first paper a plastic operation for repair of defect after removal of epithelioma of the lower lip is described for the first time. Many good x-ray pictures illustrate articles on gastric and duodenal lesions and a good description of the technic is given. Stress is laid on the relation of gastric ulcer to gastric cancer and the importance of early operation. A few illustrations give an idea of the types of operation used. Dr. Will Mayo reports three per cent of recurrences of symptoms after operations for duodenal ulcer—gastrojejunostomy having been the method of choice. He is convinced that a too coarse silk has been used in many anas-

tomoses, and he recommends a No. 0 silk. He believes that it is the silk in the outer layers of the suture that causes trouble by working into the lumen and, dangling partially free, prevents healing. He hesitates to use catgut in the outer layer as it is such a good culture medium.

Braasch reports that in 1000 patients in which uretero-pyelography has been employed there have been no fatalities and no permanent injury, 10 per cent collargol and the gravity method of injection of the warm solution being used.

Judd reports 218 cases of chronic mastitis and reviews the end results after operations for cancer of the breast. He believes that chronic cystic mastitis has a definite relation to cancer and in many instances may be considered a pre-cancerous lesion. In 7 out of 218 cases a complete breast operation with gland and muscle resection was done. He states that at times after the

complete breast operation permanent limitations of movement and swelling in the arm and shoulder occur. May this not be due to lack of care in closing the wound, so that there is tension of skin over the new axilla, thus leaving a dead space around the vessels? This space fills with blood which in the presence of a low grade infection from the skin organizes and constricts the blood vessels, resulting in considerable scar and subsequent edema and lack of function, a point strongly emphasized by Dr. Halsted.

Beckman (in writing of decortication of the lung) reports a case of an old empyema, treated by decortication, in which the entire lung expanded after being totally collapsed for two years. Decortication produces less shock than the Schede operation.

One of the most interesting of the papers is that in which Wm. Mayo writes of clinics in Germany, Belgium and Great Britain which he visited in 1913.

BOOKS RECEIVED.

Cerebellar Abscess. Its Etiology, Pathology, Diagnosis and Treatment Including Anatomy and Physiology of the Cerebellum. By Isidore Friesner, M. D., and Alfred Braun, M. D., F. A. C. S. With 10 full page plates and 16 illustrations in text. 1916. 8°. 186 pages. Paul B. Hoeber, New York.

The Diagnosis and Treatment of Heart Disease. Practical Points for Students and Practitioners. By E. M. Brockbank, M. D. (Vict.), F. R. C. P. Second edition, with illustrations. 1916. 12°. 120 pages. Paul B. Hoeber, New York.

Clinical Disorders of the Heart Beat. A Handbook for Practitioners and Students. By Thomas Lewis, M. D., D. Sc., F. R. C. P. Third edition. 1916. 8°. 116 pages. Paul B. Hoeber, New York.

Modern Medicine and Some Modern Remedies. Practical Notes for the General Practitioner. By Thomas Bodley Scott. With a Preface by Sir Lauder Brunton, Bart., F. R. S. 1916. 12°. 159 pages. Paul B. Hoeber, New York.

Mentally Deficient Children; Their Treatment and Training. By G. E. Shuttleworth, B. A., M. D., and W. A. Potts, M. A., M. D. Fourth edition. 1916. 12°. 284 pages. P. Blakiston's Son & Co., Philadelphia.

The Primary Lung Focus of Tuberculosis in Children. By Dr. Anthony Ghon. English edition. Authorized translation by D. Barty King, M. A., M. D. (Edin.), M. R. C. P. (Lond. and Edin.). With seventy-two text illustrations, one black and one colored plate. 1916. 8°. 72 pages. Paul B. Hoeber, New York.

Localization by X-Rays and Stereoscopes. By Sir James Mackenzie Davidson, M. B., C. M. Aberd. With 35 stereoscopic illustrations on special plates and other figures in the text. 1916. 8°. 72 pages. Paul B. Hoeber, New York.

The Pathology of Tumors. By E. H. Kettle, M. D., B. S., Lond. With one hundred and twenty-six illustrations. 1916. 8°. 224 pages. Paul B. Hoeber, New York.

New York Dermatological Society, 1869-1916. Constitution and By-laws. List of Members. 1916. 12°. 15 pages. New York.

Practical Massage and Corrective Exercises. By Hartvig Nissen. Revised and enlarged edition of the Author's "Practical Massage in Twenty Lessons," with many additions. With 68 original illustrations, including several full-page, half-tone plates. 1916. 12°. 211 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

Skin Cancer. By Henry H. Hazen, A. B., M. D. With ninety-seven text illustrations and one colored frontispiece. 1916. 8°. 251 pages. C. V. Mosby Company, St. Louis.

Diseases of the Digestive Tract and Their Treatment. By A. Everett Austin, A. M., M. D. With eighty-five illustrations, including ten color plates. 1916. 8°. 552 pages. C. V. Mosby Company, St. Louis.

Obstetrics, Normal and Operative. By George Peaslee Shears, B. S., M. D. 419 illustrations. 1916. 8°. 745 pages. J. B. Lippincott Company, Philadelphia and London.

Diseases of the Skin. By Richard L. Sutton, M. D. With six hundred and ninety-three illustrations and eight colored plates. 1916. 8°. 916 pages. C. V. Mosby Company, St. Louis.

The Dream Problem. By Dr. A. E. Maeder. Authorized translation by Drs. Frank Mead Hallock and Smith Ely Jelliffe. Nervous and Mental Disease Monograph Series No. 22. 1916. 8°. 43 pages. The Nervous and Mental Disease Publishing Company, New York.

Ohio State Board of Health. Twenty-ninth Annual Report of the State Board of Health of the State of Ohio for the Year Ending December 31, 1914. 1915. 8°. 894 pages. The F. J. Heer Printing Company, Columbus, Ohio.

United States Department of Commerce, Bureau of the Census. United States Life Tables 1910. Prepared under the supervision of Prof. W. Glover of the University of Michigan. 1916. 4°. 65 pages. Government Printing Office, Washington.

A Text-Book of Pathology. By W. G. MacCallum. With 575 illustrations, chiefly from the drawings of Alfred Feinberg. 1916. 8°. 1085 pages. W. B. Saunders Company, Philadelphia and London.

A Text-Book of Practical Gynecology. For Practitioners and Students. By D. Tod Gilliam, M. D., and Earl M. Gilliam, M. D. 5 rev. ed. Illustrated with 352 engravings, a colored frontispiece, and 13 full-page half-tone plates. 1916. 8°. 681 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

Harvey's Views on the Use of the Circulation of the Blood. By John G. Curtis, M. D., LL. D. Based on a Lecture Delivered in 1907 before The Johns Hopkins Hospital Historical Club at Baltimore. 1915. 12°. 194 pages. Columbia University Press, New York.

Christianity and Sex Problems. By Hugh Northcote, M. A. 2 ed., revised and enlarged. 1916. 8°. 478 pages. F. A. Davis Company, Philadelphia; Stanley Phillips, London.

BULLETIN

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THE NON-PROTEIN NITROGEN AND UREA IN THE MATERNAL AND THE FETAL BLOOD AT THE TIME OF BIRTH.

By J. MORRIS SLEMONS and WILLIAM H. MORRIS.

(From the Department of Obstetrics and Gynecology, Yale Medical School.)

Chemical analysis of the blood, which has recently been simplified and standardized to provide clinical methods for routine use, affords an approach to problems in fetal nutrition, especially the interchange of foodstuffs and waste products in the placenta. At present the explanation of these phenomena is based upon very few established facts. In their place we have hypothetical suggestions which are difficult of experimental test, for the object of study is inaccessible and the surgical operation necessary to reach it may impair, or completely destroy, the mechanism in question. Moreover, we have not possessed an analytical technique delicate enough to estimate the substances passing from the mother to the fetus, or in the opposite direction. So long as this was true, partially proven or entirely unproven theories were inevitable. Many of these still prevail, although, ultimately, they will probably be shown to be erroneous, perhaps as erroneous as the Hippocratic conception of the origin and function of the placenta.

The placenta, Hippocrates taught, was formed by coagulation of the mother's blood, and constructed so as to unite directly the maternal with the fetal circulation. The mother's blood was said to leave her body and enter the fetus, and subsequently to return whence it came. This explanation was adopted by Galen and by his successors, until, in 1564, Arantius announced his doubts as to a direct vascular connection between the two organisms. In this opinion, however, he stood alone, and although correct, his belief in the integrity of the fetal circulation was not substantiated by an objective demonstration for nearly a century.

In 1660, Harvey described the arrangement of the placental blood-vessels. As a corollary to his demonstration of a partition between the maternal and fetal circulations, some mechanism was required to effect the transfer of substances from one to the other. Consequently, Harvey assumed that the partition itself played this active rôle, performing its work not unlike the walls of the intestine perform theirs.

The existence of the placental partition was shown in the clearest way by the work of John and William Hunter. The credit due them individually is uncertain, for this investigation caused bitter strife between the brothers, and conflicting claims arose. Together, at least, by injecting both uterine and umbilical vessels, they secured unquestionable proof that the mother's blood never entered the fetus, and also that the reverse phenomenon was impossible.

With the help of the microscope and modern histological technique, the anatomical character of the placental partition became established. And, too, there is no longer a question of the path followed by the fetal blood. The two umbilical arteries containing venous blood, enter the placenta from the cord, dividing again and again to form a multitude of capillaries; subsequently, these reunite into a single vessel, the umbilical vein, through which the arterialized blood returns to the fetus.

An extensive vascular bed, chiefly secured by division of the larger fetal vessels into a myriad of smaller ones, is further enlarged by the arrangement of the smallest of these; they form loops which hang toward the maternal blood. The

vascular loops surrounded by connective tissue, which in turn is covered by epithelium, constitute the chorionic villi. These tiny, finger-like projections are immersed in lakes of maternal blood. They act both as receptors of nutriment for the fetus and as its excretory agents. Beyond these facts, knowledge of the physiology of the villi is fragmentary. How substances pass from one circulation to the other through the layers of chorionic connective tissue and epithelium—which, together with the wall of the fetal vessels, constitute the placental partition—is a question answered, thus far, only hypothetically.

1. *The Vitalistic Hypothesis.*—Active participation by the placenta in the preparation of fetal nutriment, as has been said, was first suggested by William Harvey. And recently, his view, amplified to accord with the prevailing theory of ferments, has been the popular one, for Hofbauer and others have demonstrated the presence of enzymes in placental tissue. However, it has not been shown that these lipolytic, diastatic, and proteolytic enzymes are direct agents in the interchange of substances between mother and fetus. They may be connected only with the living processes of the placental tissue.

2. *The Mechanistic Hypothesis.*—In the transmission of some substances a passive part is taken by the placenta which, in other words, behaves as a permeable membrane. Oxygen and carbon dioxide, as we are taught by the experiments of Cohnstein and Zuntz, will pass equally well from mother to fetus or in the opposite direction. Probably, the laws of diffusion also hold true for other gases, as chloroform, ether, and nitrous oxide; but they do not apply to gases like carbon monoxide which enter into chemical combination with hæmoglobin. Cohnstein and Zuntz found, too, that sodium chloride passed the placenta by osmosis. The evidence regarding the transmission of glucose was not conclusive, but here also these investigators believed that the placenta took no active part.

One fact regarding placental transmission was firmly established by the experiments of Gusserow and his associates; provided the placenta was normal, no insoluble substance could pass it. Consequently, it was admitted that the formed elements of the blood were confined to that circulation in which they originated. Women suffering from leukæmia bear infants that present a normal blood picture. And, experimentally, it has been demonstrated that cinnabar, barium sulphate, and other insoluble compounds introduced either into mother or fetus were completely arrested by the placental partition. On the other hand, a variety of soluble substances injected into the mother may be detected in the fetus. From reports of such experiments Kehrér stated in 1907 that 43 substances out of 73 tested passed readily to the fetus. Similarly, many will pass in the opposite direction. Those known to do so are chiefly poisons selected for study, because a toxic action upon the maternal animal assists in determining the result of an experiment. Strychnin, hydrocyanic acid, nicotin, curare, pilocarpin, physostigmin, phlorhizin, sodium sulphate, methylene blue, and epinephrin injected into the fetus enter the maternal circulation.

Except in the case of carbon dioxide, the elimination of fetal waste products through the placenta has not been the subject of serious investigation. From three analyses in which the

same quantity of urea was found in the blood of the mother and her newborn infant, Morel and Mouriquand concluded that the placenta was not a barrier to its transmission. And Bang in a long series of analyses included a few samples of blood from the umbilical cord. But beyond brief and casual comments, there are no data regarding the placental elimination of waste products. The suggestion of Halban and Fleck, that the chorionic villi elaborate an internal secretion which controls fetal excretion, rests entirely upon theoretical considerations. "At present," we read in Döderlein's *Handbuch der Geburtshilfe* (1915), "it is impossible to say more than that fetal waste products make their way to the placenta and through it reach the maternal organism, which subsequently eliminates them."

Since there is little known of the principles involved in the placental interchange and since direct study of the problem by animal experimentation may introduce artificial factors, we have sought clinical data from which the character of this mechanism could be inferred. In this communication we consider the results of analyses to determine the non-protein nitrogen and the urea in the maternal and the fetal blood. As nearly as possible the specimens were obtained simultaneously, just after the birth occurred; in other words, at the end of the second stage of labor. Usually, the fetal blood was secured first, but at most only a few minutes before the maternal. The former was collected from the placental end of the severed umbilical cord which bled into a sterile flask; the latter was aspirated from a vein in the mother's forearm.

A number of analyses indicated that the fetal blood was derived exclusively from the umbilical vein; a result to be expected from the anatomical structure of the umbilical vessels. The two arteries conducting blood from the fetus to the placenta are supplied with thick, muscular coats which, after the infant is born, contract firmly and completely close these vessels. The umbilical vein, on the contrary, remains patent until thrombosis occurs, and consequently hemorrhage from the cord always comes from this source. The analytical results yielded by the blood flowing from the severed end of the cord, and by the blood aspirated from the umbilical vein were identical—a fact which corroborates the conclusion that we were dealing with specimens of blood from the umbilical vein. In the case of the fetus, then, the sample of blood was arterial and came directly from the placenta.

The maternal blood after leaving the placenta had passed through the heart, the lungs and the hand, before a specimen for analysis was secured. During this course, probably there was no change which could be detected by the analytical methods employed. Professor Otto Folin in a personal communication has expressed this opinion regarding the non-protein nitrogen; and Marshall and Davis found the same values for urea in various organs of the body. Moreover, we have compared specimens from the vena cava* and from the peripheral circulation of dogs anesthetized with ether and

* The caliber of the uterine veins was so small that a specimen sufficient for analysis could not be aspirated.

found practically no difference between them. The following result is typical:

Blood from	Rest-nitrogen.	Urea-nitrogen.	Percentage of urea-nitrogen.
Vena cava.	34.9 mg.	20.5 mg.	58 per cent.
Femoral vein.	34.5 mg.	19.3 mg.	58 per cent.

In human subjects, then, we assume a corresponding resemblance between the peripheral and the uterine blood. If there is any difference between the non-protein nitrogen of the blood in the uterine veins and that in the veins of the forearm, it must be very small. The following results, therefore, fairly represent the composition of the blood which in one instance had just left the fetal side of the placenta and in the other instance the maternal side. This inference was verified by an experiment, the details of which will be given later.

The analytical method employed for the estimation of nitrogen was that devised by Folin and Denis. It consists essentially in removing the protein by precipitation with methyl alcohol, and following this procedure with a Kjeldahl on the filtrate. The latter step determines the non-protein or rest-nitrogen of the blood.

The urea was estimated by the urease method of Marshall, with the apparatus devised by Van Slyke and Cullen. The values thus obtained actually include the ammonia, but in normal cases this is of an amount too insignificant for consideration.

The analytical results for both rest-nitrogen and urea-nitrogen are always stated in terms of milligrams of the substance per 100 cc. of blood.

NORMAL CASES.

I PARA.

Number.	Source.	Age of mother.	Length of labor.	Rest-nitrogen.	Urea-nitrogen.	Percentage of urea-n.	Remarks.
1	Mother..	22	12 hrs.	20.2	9.3	46%	No anæsthetic.
	Fetus...			20.5	8.9	43%	
2	Mother..	19	11 hrs.	21.5	9.3	43%	" "
	Fetus...			24.0	9.3	43%	
3	Mother..	27	53 hrs.	26.8	9.3	42%	" "
	Fetus...			28.5	9.3	42%	
4	Mother..	26	50 hrs.	26.5	9.8	37%	Whiffs of chloroform.
	Fetus...			27.2	10.7	39%	
5	Mother..	19	12 hrs.	21.7	9.3	43%	" "
	Fetus...			20.0	8.4	42%	
6	Mother..	22	18 hrs.	25.0	9.3	43%	" "
	Fetus...			27.2	9.3	43%	
7	Mother..	28	16½ hrs.	21.0	9.3	43%	" "
	Fetus...			21.5	9.3	43%	
8	Mother..	25	12 hrs.	33.5	9.3	43%	" "
	Fetus...			34.2	9.3	43%	
9	Mother..	19	5½ hrs.	33.1	9.3	43%	" "
	Fetus...			32.5	9.3	43%	
10	Mother..	31	27½ hrs.	20.5	9.3	43%	" "
	Fetus...			22.0	9.3	43%	
11	Mother..	29	27 hrs.	20.0	9.8	50%	Deep chloroform.
	Fetus...			19.0	11.7	61%	
12	Mother..	24	18 hrs.	23.0	9.3	43%	Nitrous oxide.
	Fetus...			23.0	9.3	43%	
13	Mother..	20	10 hrs.	26.0	9.3	43%	Morphine and tyramine.
	Fetus...			23.0	9.3	43%	
14	Mother..	20	19 hrs.	27.5	9.3	43%	" " "
	Fetus...			28.9	9.3	43%	

II PARA.

15	Mother..	32	4 hrs.	22.5	9.8	44%	No anæsthetic.
	Fetus...			22.0	9.8	45%	
16	Mother..	28	9½ hrs.	23.5	10.3	44%	" "
	Fetus...			20.0	8.9	43%	
17	Mother..	25	5 hrs.	21.7	10.2	47%	" "
	Fetus...			21.7	9.3	43%	
18	Mother..	25	9 hrs.	22.3	9.3	43%	" "
	Fetus...			22.5	9.3	43%	
19	Mother..	25	12 hrs.	21.2	8.9	42%	Whiffs of chloroform.
	Fetus...			22.5	10.3	46%	
20	Mother..	22	7 hrs.	28.2	13.5	51%	" "
	Fetus...			26.5	12.1	46%	
21	Mother..	25	9½ hrs.	19.5	8.4	43%	" "
	Fetus...			19.2	7.9	41%	
22	Mother..	22	8 hrs.	18.5	8.4	45%	" "
	Fetus...			18.5	9.3	50%	
23	Mother..	28	9½ hrs.	32.7	9.3	43%	" "
	Fetus...			30.8	9.3	43%	
24	Mother..	26	8 hrs.	26.2	9.3	43%	" "
	Fetus...			24.5	9.3	43%	

III PARA.

25	Mother..	24	6½ hrs.	23.5	9.3	43%	No anæsthetic.
	Fetus...			23.7	9.3	43%	
26	Mother..	22	15 hrs.	25.0	9.3	43%	" "
	Fetus...			26.2	9.3	43%	
27	Mother..	34	4 hrs.	26.5	10.8	41%	Whiffs of chloroform.
	Fetus...			27.5	11.7	43%	

IV PARA.

28	Mother..	33	4 hrs.	25.7	9.3	43%	No anæsthetic.
	Fetus...			24.5	9.3	43%	
29	Mother..	36	38 hrs.	27.7	13.1	47%	Whiffs of chloroform.
	Fetus...			27.2	13.5	50%	

V PARA.

30	Mother..	34	4 hrs.	25.3	9.3	43%	No anæsthetic.
	Fetus...			25.7	9.3	43%	
31	Mother..	30	11 hrs.	29.7	14.0	47%	Whiffs of chloroform.
	Fetus...			24.2	13.5	55%	

VII PARA.

32	Mother..	34	10 hrs.	30.0	9.3	43%	No anæsthetic.
	Fetus(1)			30.2	9.3	43%	Twins at term.
	Fetus(2)			30.2	9.3	43%	Normal infants.

VIII PARA.

33	Mother..	39	18 hrs.	27.7	11.2	40%	No anæsthetic.
	Fetus...			24.7	9.8	40%	
34	Mother..	39	7 hrs.	32.0	9.3	43%	Whiffs of chloroform.
	Fetus...			32.0	9.3	43%	

IX PARA.

35	Mother..	35	15 hrs.	27.7	12.6	45%	Whiffs of chloroform.
	Fetus...			27.5	11.7	43%	

* The figures in this column indicate the amount of rest-nitrogen which is in the form of urea.

Normal values for the non-protein or rest-nitrogen have been established by the consistent results of several investigators, and it appears that during pregnancy the same values

are normal as at other times. In healthy subjects Folin and Denis found from 22 to 26 mg. of rest-nitrogen per 100 cc. of blood. Almost identical results were obtained by Tileston and Comfort, who also demonstrated a rise of 1 or 5 mg. after meals. In non-pregnant women between the ages of 21 and 35 years, Bang observed from 19 to 28 mg.; the average calculated from eight analyses was 23.2 mg.

On the other hand, Landsberg found in 18 cases of uncomplicated pregnancy that the average quantity of rest-nitrogen was 24 mg. A similar result is recorded by Farr and Williams on the basis of eight analyses. The higher figure of Plass, 34.7 mg., is almost certainly explained by the analytical method employed. Our experience indicates that normally the non-protein nitrogen of the blood is quantitatively the same in pregnant and non-pregnant women; and, furthermore, that there is no noteworthy change at the time of labor.

REST-N. OF MATERNAL BLOOD DURING LABOR.

Onset of labor.	End of 2d stage.	Interval between analyses.
mg.	mg.	hrs.
18.5	20.5	27 1/2
18.7	23.5	9 1/2
26.0	25.0	15
26.7	28.2	7

A series of 35 cases in which a normal pregnancy terminated with spontaneous delivery was studied, and we found that immediately after the fetus was born specimens of the mother's blood contained from 18.5 to 33.5 mg. of non-protein nitrogen. The average was 25.2 mg. So closely does this result agree with the accepted normal that it may seem superfluous to remark that the question of an error referable to the digestion of food does not enter here. Patients have no desire for food during the active part of labor. Our analyses, therefore, are comparable with others which have been made after a suitable period of fasting. Generally, the values fell between 20 and 30 mg., like those previously given for healthy men and women; lower results were obtained twice and higher ones three times.

It is instructive that the duration of labor is without influence upon the rest-nitrogen, for indirectly this fact is re-

AVERAGE REST-NITROGEN ACCORDING TO PARITY.

Para.	Rest-nitrogen.	Number of cases.
	mg.	
I.	24.8	14
II.	23.8	10
III.	25.0	3
IV.	26.7	2
V.	27.5	1
VII.	30.0	2
VIII.	29.8	2
IX.	27.5	1

lated to the problem of eclampsia. That eclampsia depends upon a retention of nitrogenous waste products is a currently accepted hypothesis; and clinical experience teaches that convulsions develop more frequently when labor is prolonged. As there is no nitrogen retention when labor is prolonged, the

predisposing factor to eclampsia must lie elsewhere. However, this evidence against the nitrogen hypothesis is indirect, and for its value depends upon the confirmation it gives to analyses made in the course of the disease.

The non-protein nitrogen of the blood does not vary with the age of the patient, nor with the number of previous pregnancies. Although the following table indicates a tendency toward an increase in the rest-nitrogen for successive pregnancies, healthy primiparous women, 20 to 25 years of age, presented even higher values than a patient in her ninth labor.

In the fetus, we found practically the same amount of rest-nitrogen as in the mother; the average of 36 determinations was 24.9 mg. Similarly, the extremes encountered (18.5 and 34.2 mg.) correspond with those of the mother's blood. When the cases are examined individually, the very close resemblance between them becomes most apparent. Results differing by not more than a milligram appear in 20 instances; and the maternal rest-nitrogen was slightly higher than the fetal in 9 instances, and slightly lower in 6. Usually the difference was less than 2 mg. per 100 cc.; it was 5.5 mg. at most. A case of twins follows the rule and perhaps best illustrates it: the mother's blood contained 30 mg., that of each fetus 30.2 mg.

It is reasonably certain that all the constituents of the non-protein blood nitrogen may pass through the placenta, for they belong either to the class of foods or of waste products. The fetus acquires its nitrogenous food from the mother and after utilization the resulting waste is transferred to her circulation. Equal values for the rest-nitrogen on both sides of the placental partition indicate a free interchange of these substances, probably by diffusion. Accordingly, active participation of the placental partition would not be required: the interchange of a substance would depend merely upon its concentration in each circulation. The interpretation of the analytical results certainly does not require the agency of placental enzymes. But before diffusion is accepted as the explanation for the placental interchange of non-protein nitrogen, each of its constituents—urea, ammonia, uric acid, creatinin, and amino acids—should be studied separately. As regards the urea and ammonia, we have data which demonstrate that these substances diffuse readily through the human placenta.

The urease method, as we have said, yields results which embrace both the urea and the ammonia, but normally the blood contains an extremely small quantity of the latter, which, therefore, may be disregarded. Conforming to the custom adopted in similar reports we designate the urease determinations, "urea-nitrogen." Yet, for our purpose, they have a broader significance, indicating that not only the urea but also the ammonia of the blood passes the placenta by diffusion.

In 16 normal cases at the moment of birth the average quantity of urea-nitrogen in the mother's blood was 10.5 mg.; and in the fetal blood 10.1 mg. The extremes encountered corresponded closely; in the mother they were 8.4 and 14.0 mg., and in the fetus 7.9 and 13.5 mg. And again, examined case by case, the urea values in mother and fetus are equivalent. Thus, the determinations were identical in 11 instances, while

there was slightly more maternal urea in 3 instances and slightly more fetal urea in 2. The maximal difference between them was 1.9 mg. per 100 cc.

UREA-NITROGEN IN MATERNAL AND FETAL BLOOD AT THE MOMENT OF BIRTH.			
Para.	Mother.	Fetus.	Number of cases.
	mg.	mg.	
I.	9.6	9.9	4
II.	9.9	9.7	7
III.	10.8	11.7	1
IV.	13.1	13.5	1
V.	14.0	13.5	1
VIII.	11.2	9.8	1
IX.	12.6	11.7	1

There is abundant evidence to show that urea is a readily diffusible substance in the animal body. Bang found equal quantities in corpuscles and plasma. Marshall and Davis demonstrated that the same concentration existed in the blood and tissues, both normally and after large injections of urea. The latter investigators concluded that diffusion was almost instantaneous and after 15 minutes was complete. Upon these premises it would be fair to assume that the analytical results obtained from the blood of the arm veins also applied to the blood in the uterine veins, returning from the placenta after participation in the interchange between mother and fetus. But we have verified the accuracy of this assumption. In the case of an etherized dog near term, specimens of blood from the uterine and umbilical veins were analyzed. The results confirm our clinical observations and also agree with two experiments upon rabbits made by Morel and Mouriquand, though these investigators do not mention the source of their specimens.

MATERNAL AND FETAL BLOOD OF DOG.*			
Source.	Rest-nitrogen.	Urea-nitrogen.	Per cent urea.
Uterine vein . . .	40.0 mg.	16.4 mg.	41
Umbilical vein . .	41.5 mg.	16.4 mg.	39

* Higher values occur in dogs because they are carnivorous.

Normally, then, the same concentration of urea exists in the maternal and fetal circulations; and this is also true of the ammonia, for the analytical method yields results that include both substances. Maintenance of this equilibrium requires the freedom of movement permitted by diffusion. Indeed, the question of an enzyme action can scarcely come into consideration, since there is no notable difference in the urea concentration on the two sides of the placenta.

Morel and Mouriquand also obtained similar values for the amino acids in maternal and fetal blood; and consequently stated that the placenta is not a barrier to the passage of nitrogenous crystalloids. In this laboratory, Morse has estimated the amino-acid nitrogen in the blood of mother and fetus; and though his results, which will soon be published, suggest that that problem is more complex than the urea problem, it appears that maternal and fetal blood contain equivalent amounts of amino acids. Creatinin and uric acid remain unstudied.

It is noteworthy that at the time of labor the quantity of urea in the blood is the same as during pregnancy, and that this quantity is somewhat less than the accepted normal. Employing the urease method, Schwartz and McGill found 12.9 mg. the average for healthy subjects; with other methods Folin and Denis found 11-13 mg., Tileston and Comfort 12-14 mg. Bang found 12.3 mg. as the average for eight normal women. On the other hand, Farr and Williams obtained 10.7 mg. during pregnancy, which is practically the average calculated from our series of normal labors.

In healthy men and women, the urea includes approximately 50 per cent of the total non-protein nitrogen, but at the time of labor this percentage is smaller. For the mother the urea represented 44 per cent of the rest-nitrogen and for the fetus 45 per cent. The latter figure closely resembles the average which Leopold and Bernhard found in children. There the rest-nitrogen was 28 mg., the urea-nitrogen 12 mg., and consequently the ratio between them was 43 per cent.

ABNORMAL CASES. OBSTETRICAL OPERATIONS.									
Number.	Source.	Age of mother.	Duration of labor.	Rest. Nitrogen.	Urea-nitrogen.	Percent urea.	Remarks.		
		years.	hrs. mts.	mg.	mg.				
36	Mother.	27	9½	22.7	11.2	49	Low forceps; chloroform.		
	Fetus.	11p.		22.7	11.2	49	Normal infant.		
37	Mother.	20	2½	20.5	12.6	61	Mid-forceps; chloroform.		
	Fetus.	1p.		20.5	14.9	72	Cord about neck; resuscitated.		
38	Mother.	25	48	37.5	28.0	74	Attempts at forceps; prolonged chloroform. Craniotomy.		
	Fetus.	1p.		36.0	30.1	85			
39	Mother.	28	13	26.5	14.9	56	Spontaneous delivery; deep chloroform.		
	Fetus.	11p.		21.0	14.9	71	chloroform; asphyxiat. infant.		
40	Mother.	22	48	27.0	13.5	50	Low forceps; ether.		
	Fetus.	1p.		30.0	14.1	47	Normal infant.		
41	Mother.	22	54½	25.5	11.7	46	Breech. Chloroform.		
	Fetus.	1p.		20.2	13.1	65	Still-birth.		
42	Mother.	24	24	34.2	Breech. Chloroform.		
	Fetus.	IVp.		34.2	Normal infant.		
43	Mother.	35	9	21.2	15.8	74	Version. Chloroform.		
	Fetus.	Vp.		24.2	15.8	65	Still-birth.		

PREGNANCY TOXÆMIAS.									
44	Mother.	20	28	21.2	13.1	61	Pre-eclamptic tox. Forceps.		
	Fetus.	1p.		22.7	12.6	55	Healthy, premature infant.		
45	Mother.	35	...	34.0	30.1	88	Pre-eclamptic tx. Hysterotomy.		
	Fetus.	11p.		35.5	26.1	74	Premature.		
46	Mother.	33	...	31.0	12.6	46	Eclampsia; Caesarian; ether.		
	Fetus.	111p.		30.7	Premature.		
47	Mother.	24	16	45.7	28.4	62	Eclampsia; high forceps. Died.		
	Fetus.	1p.		43.5	27.1	62	Still-birth.		
48	Mother.	42	8	33.3	Chr. nephritis. Mid-forceps.		
	Fetus.	XIIp.		40.0	Still-birth.		
49	Mother.	42	6	...	18.2	...	Chr. nephritis; normal labor.		
	Fetus.	XIIIp.		...	16.8	...	Normal infant.		

SYPHILIS.									
50	Mother.	20	8½	24.0	13.6	57	At term.		
	Fetus.	1p.		24.0	14.0	58	Infant alive.		
51	Mother.	21	11½	21.2	11.0	51	At term.		
	Fetus.	1p.		20.0	10.4	51	Infant alive.		
52	Mother.	20	6½	...	20.7	...	Premature delivery, 7th month.		
	Fetus.	11p.		...	20.1	...	Died shortly after its birth.		
53	Mother.	19	22½	27.0	14.9	55	Wassermann neg.; placenta syphilitic.		
	Fetus.	1p.		24.5	14.0	57	Infant normal.		

PSYCHOSIS.

54	Mother.	36	12	25.0	14.9	60	Imbecile mother.
	Fetus..	1p.		25.0	14.9	60	Premature, poorly nourished.

CARDIAC LESIONS.

55	Mother.	22	16	28.7	17.7	62	Mitral and aortic regurgitation.
	Fetus..	1p.		21.7	14.9	54	Normal infant.

STILL-BORN INFANTS.

56	Fetus..	60	22.5	14.0	62	Face presentation; forceps.
57	Fetus..	62	20.7	15.4	74	Mid-forceps; chloroform.
58	Fetus..	50	26.7	13.0	49	Enlarged thymus.

AVERAGE OF NORMAL CASES *with* and *without* CHLOROFORM.

	Rest-nitrogen.		Urea-nitrogen.		Percentage of urea-nitrogen.	
	Mother.	Fetus.	Mother.	Fetus.	Mother.	Fetus.
No anaesthesia.....	23.1	21.6	10.1	9.3	44	43
Whiffs of chloroform.....	24.3	23.6	10.5	10.9	43	46

In a number of instances in which complications existed we have had the opportunity to make observations comparable with those made during normal labor. Thus data were obtained relating to chloroform anaesthesia, obstetrical operations, syphilis, the autointoxications of pregnancy, and asphyxiation of the fetus during delivery. On their own account, these results were instructive and also because they gave additional information regarding the problem of the placental interchange.

Chloroform anaesthesia interferes with the nitrogenous exchange between mother and fetus, not when administered in whiffs as customarily at the conclusion of the expulsive stage of labor, but if given to maintain deeper anaesthesia. The effect varies with the depth and the duration of narcosis. Among cases in the normal series some of the deliveries were conducted without an anaesthetic, others with chloroform. The averages of these groups are not unlike, and demonstrate that the effect of the (so-called) obstetrical degree of chloroform narcosis upon the non-protein nitrogen of the blood is negligible. Somewhat deeper anaesthesia also is attended only with slight alterations in the composition of the fetal blood. Case 11 illustrates this point. For 15 minutes before the birth the mother was completely anaesthetized; the infant was not asphyxiated; its blood contained a normal amount of rest-nitrogen and 61 per cent of urea-nitrogen. Although less conspicuous, a tendency for the urea to increase is apparent in the average of the normal cases given chloroform. This feature is pronounced in Case 39 (71 per cent of fetal urea-nitrogen) where fetal asphyxia was relieved only after vigorous resuscitative measures.

Surgical anaesthesia is accompanied with an elevation also in the maternal urea, and ultimately with increase of the non-protein nitrogen in both circulations. Case 38 exemplifies these effects. In this instance, before the patient entered the

hospital, several attempts with forceps had been made and she had been under chloroform for a period of about two hours. The maternal nitrogen was 37.5 mg., and the urea-nitrogen 28 mg., the fetal nitrogen was 36 mg. and the urea-nitrogen 30.8 mg. Whether these effects are partially to be explained by the operative procedure is a question difficult to answer, but generally such changes are not the sequel of a forceps operation. For example, Case 36 presents only a slight increase in urea, which corresponds with that referable to the use of chloroform in normal cases.

From our observations, then, it appears that at first chloroform merely increases the fetal urea. This phenomenon we do not attribute to an increased production of urea in the fetus but to a diminished rate of diffusion through the placenta. Clinically, it is known that chloroform slows the fetal heart and consequently in a given length of time a smaller quantity of blood reaches the placenta. In these circumstances, obviously, fetal urea has less opportunity for excretion. Later, principally because of urea retention, the rest-nitrogen of the fetal blood increases. Irrespective of the fetus, deep chloroform anaesthesia finally causes an increase of both urea and rest-nitrogen in the maternal circulation. However, even with prolonged anaesthesia the effect upon the fetus is the more pronounced.

In cases in which low forceps operations were performed because the expulsive forces were insufficient, we found nothing notable beyond the initial, mild effects of chloroform. After this operation, indeed, we found less marked changes in the fetal blood than when pituitrin was used to augment uterine contractions. Thus, in a case of the latter kind, the fetal urea was 14 mg., whereas after low forceps we observed 11.2 and 11.7 mg. On the other hand with medium and high forceps, requiring deeper and more prolonged anaesthesia, the fetal urea-nitrogen amounted to 13, 14, and 15 mg.

As anyone would predict, we found that coils of cord about the neck of the fetus constricting the umbilical vessels caused retention of urea in the fetal circulation. This occurred in Case 37, although the interpretation of the analysis is complicated by the fact that the patient was deeply anaesthetized. A more marked contrast between mother and fetus existed in the case (No. 41) of breech extraction, where the umbilical circulation was shut off for several minutes and the fetus was still-born.

During the autointoxication which precedes eclampsia and also after the development of convulsions, blood analyses have failed, thus far, to render assistance toward either treatment or prognosis. At times, though not invariably, there is a moderate increase in the non-protein nitrogen—a phenomenon that must be explained by the degree of renal involvement. In this sense, Cases 44 and 45 present an interesting contrast. The former was a typical case of pre-eclamptic toxæmia with moderate elevation of blood-pressure and mild albuminuria. The latter patient suffered from a pronounced renal disturbance; the urine contained 10 gm. of albumin per liter and the systolic pressure was 200 mm. of mercury. In the first case, though the urea (13 mg.) was slightly increased, the rest-

nitrogen (21 mg.) was normal; in the second case the urea was 30 mg. and the rest-nitrogen 34 mg.

With regard to placental transmission, cases of renal insufficiency demonstrate that high urea values in the maternal circulation are accompanied by corresponding values in the fetal circulation; a finding which confirms the conclusion that urea passes the placenta by diffusion. Furthermore, in other pathological conditions attended by an increase in the maternal blood-urea, a similar increase appears in the fetus. Whether the fetal values are explained by the passage of urea from mother to fetus—as Cohnstein and Zuntz showed to be possible in the case of carbon dioxide—or whether the high concentration of urea in the mother's blood merely prevents diffusion in the normal direction, is a question to be settled by animal experimentation. However, in either event the result for the fetus is the same and means an impairment of the placental excretory function. Clearly, this may be of a degree to cause intrauterine death, a well-known complication in cases of nephritic toxæmia, which occurred in Case 48.

As already observed by Tileston and Comfort and by Schwartz and McGill, abnormally large quantities of urea occur in syphilitic patients, yet not without exception (Case 51). Our chief interest is in the fact that when the mother presents the phenomenon, so does the fetus. And, similarly, in Case 54, in which the mother was suffering from an undetermined organic disturbance—probably of the ductless glands—with consequent low mentality, placental diffusion satisfactorily accounts for the duplication in the fetus of a high maternal urea.

The analyses in a case (No. 55) of combined mitral and aortic disease are noteworthy. About eight weeks before confinement compensation had been broken but later was restored. Toward the end of labor the patient became exhausted. Much higher urea values than were present in this instance (17.7 mg.) have been shown to be due to cardiac decompensation by Foster, by Rountree, Marshall and Baetjer and by Schwartz and McGill. The maternal heart action must also account for an increase in the fetal urea, since at birth and subsequently the infant's physical condition was excellent.

ASPHYXIATED AND STILL-BORN INFANTS.

No.	Rest-nitrogen.	Urea-nitrogen.	Percentage of urea-nitrogen.	Remarks.
	mg.	mg.		
37	20.5	14.9	72	Cord about neck; resuscitated.
39	21.0	14.9	71	Mid-forceps; resuscitated.
57	36.0	30.1	85	Mid-forceps; still-born.
38	20.7	15.4	74	High forceps; still-born.
41	20.2	13.1	65	Breech; still-born.
43	24.2	15.8	65	Version; still-born.
48	40.0	Nephritic tox.; still-born.
56	22.5	14.0	62	Face presentation; still-born.
58	26.7	13.0	49	Enlarged thymus.

In cases of fetal asphyxia and still-birth the results of the blood analyses are consistent and indicate that, although the non-protein nitrogen is generally of normal amount, the urea is increased. These facts are best explained by the circulatory

phenomena which accompany fetal death. Slowing of the fetal heart, as we have said, lessens the rate at which the fetal blood flows through the placenta, and correspondingly impedes the placental interchange. At first, urea is retained in the fetal blood without increasing the rest-nitrogen, for probably the excess of urea is counterbalanced by a deficiency in amino acids, the supply of which is curtailed when the fetal circulation becomes less active. Subsequently, an increase in urea causes an increase in the rest-nitrogen.

While the average quantity of urea-nitrogen in normal fetal blood is 10.5 mg. the lowest estimate among six still-born infants was 13 mg., the highest 30 mg. However, there was not a sharp line between cases of asphyxia and still-birth; 15 mg. were found in each of two asphyxiated infants which were resuscitated, and this was a larger quantity than obtained in three of the still-births.

Besides circulatory impairment, other causes of fetal asphyxia, as in Case 58, occasionally are met with. In this case the fetal heart was beating normally at birth, but the infant could not be made to breathe. An autopsy disclosed a thymus several times the normal size. Thymic death, it would seem, depends upon the respiratory center, not upon a circulatory disturbance, for the heart was active half an hour after the birth. Moreover, the relationship between the urea and rest-nitrogen was not abnormal; there were 13 mg. of urea-nitrogen, representing 49 per cent of the rest-nitrogen. On the other hand, with circulatory impairment the urea has represented from 60 to 85 per cent of the rest-nitrogen in the fetal blood.

SUMMARY.

1. In 35 normal obstetrical patients at the time of birth the average rest-nitrogen in the maternal blood was 25.2 mg. per 100 cc. (extremes 18.5-33.5 mg.); in the fetal blood the average was 24.9 mg. (extremes 19-34.2 mg.).

2. In 16 normal patients the average quantity of urea-nitrogen in the maternal blood was 10.5 mg. per 100 cc. (extremes 8.4-14 mg.); in the fetal blood the average was 10.4 mg. (extremes 7.9-13.5 mg.).

3. The urea-nitrogen represented 44 per cent of the rest-nitrogen in the maternal and 45 per cent in the fetal blood.

4. The same concentration of urea in both circulations indicates that this substance passes through the placenta by diffusion.

5. Before this is said of the rest-nitrogen, each of its constituents should be studied separately, though it appears that equalization of the rest-nitrogen is normally maintained on the two sides of the placental partition.

6. Complications accompanied by an increase of urea in the maternal blood—toxæmias of pregnancy, syphilis, decompensated heart lesions, and others—are also attended with a corresponding increase in the fetal blood-urea. Pathological cases thus confirm the conclusion that urea diffuses through the placenta.

7. The administration of chloroform during pregnancy causes alterations first in the fetal and later in the maternal blood. Primarily the fetal blood-urea is increased. Prolonged

anæsthesia causes a moderate increase in the rest-nitrogen of both circulations.

8. Asphyxia dependent upon impairment of the fetal heart-action is attended with a notable increase in the urea of the fetal blood. In cases of still-birth this generally represents 60 to 85 per cent of the rest-nitrogen.

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TYPES OF LESION IN CHRONIC PASSIVE CONGESTION OF THE LIVER.

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It is generally recognized that the so-called "nutmeg liver" of chronic passive congestion presents a varied microscopic picture. Indeed, two livers, which to any but the most experienced observer are identical in gross appearances, may show most striking histological differences. In one the lesion may consist of a marked dilatation of the capillaries, especially in the immediate neighborhood of the central vein, with an elongation and narrowing of the intervening liver cells; in the other, the liver cells of the inner half or two-thirds of the lobule may have entirely disappeared, this area being occupied by blood, reticulum and occasional pigmented endothelial cells. The study of even a limited number of livers from cases of cardiac decompensation will soon convince one that these two types of lesion constitute by no means the only possibilities.

The object of the present study was first to classify, if possible, the varied liver lesions in chronic passive congestion. This accomplished, we attempted to determine the conditions responsible for the development of the different types, through a consideration of both clinical and autopsy findings.

Before describing the results of our investigations a brief statement of the present teaching regarding the character of

the liver lesions in chronic passive congestion, and their pathogenesis, will be briefly presented, together with a review of the more important contributions to this subject.

It was for a long time the accepted view that the disappearance of the liver cells in advanced chronic passive congestion resulted from increased blood pressure in the capillaries. Among the adherents of this theory may be mentioned Orth, Birch-Hirschfeld, Marchand and Kaufmann. Ribbert was among the first to recognize the objection that increased blood pressure must be transmitted throughout the lobule, and obviously cannot be higher in the center than in the periphery; its effect should, therefore, be diffuse, whereas it is the central portion of the lobule that regularly suffers most in chronic passive congestion. Ribbert pointed out further that the cells that succumb are those farthest removed from the blood supply, and suggested that these cells suffered from malnutrition resulting from stasis, which rendered them more susceptible to increased pressure. The process is thus regarded by him as a combined starvation and pressure atrophy. Other authors, including Sternberg and Eisenmenger, have in a general way accepted Ribbert's dualistic theory, putting emphasis on one or the other of the two factors.

The formation of fibrin thrombi in the liver capillaries, favored by the retardation of the blood flow, has been suggested as the cause of the death of the liver cells in chronic stasis, but Hart,

Hajami, Mallory and L'Engle, agree in regarding the thrombus formation as the effect rather than the cause of the necrosis. L'Engle, indeed, believes that the fibrin plugs are formed after death. In our cases thrombi were commonly met with, but they were not a constant finding, and were not associated with any particular type of lesion.

Mallory has recently brought forward an entirely new interpretation of the changes in the liver in chronic passive congestion, and goes further than Ribbert, Eisenmenger and Sternberg in minimizing the effect of increased blood pressure. He maintains that blood pressure is not a factor at all. In his opinion, based on a clinical and pathological study of a large number of cases, the disappearance of the liver cells is practically always the result of a toxic necrosis, and the stasis is only a contributory factor. He points out that while long continued stasis may lead to extreme dilatation of the sinusoids, the flattening out of the intervening liver cells, and complete atrophy or necrosis, probably never take place as the result of increased blood pressure alone. "Necrosis" he states, "is due to toxic substances (chiefly of infectious origin) in the circulation, acting apparently to some extent in combination with malnutrition. In many instances the necrosis complicating chronic passive congestion is due to the terminal infection which causes death. In others, the necrosis and disappearance of the liver cells dates back to some infection which occurred months or years previously." Mallory points out, in support of this view, that in acute infections (especially streptococci) not associated with stasis, degenerative changes in the liver cells about the center of the lobule are frequently seen. He grants that the hemorrhagic character of the lesion is the result of stasis, since the blood from the distended capillaries pours readily into the ruptured trabecular spaces—among the dead and disintegrating liver cells. The familiar picture of hemorrhagic necrosis is the result.

This new interpretation of the pathogenesis of the lesion of chronic passive congestion has met with ready acceptance by Heinrichsdorff, in a recent paper. Bolton, however, on the basis of experimental studies, concludes that stasis, with resulting malnutrition, is the essential cause of the disappearance of the liver cells. He produced a condition of chronic stasis in monkeys and cats by incomplete obstruction of the inferior vena cava. The typical picture of chronic passive congestion resulted, ending in central necrosis with hemorrhage. His animals remained perfectly healthy throughout the experiments and showed no evidence whatever of infection. Oertel, who has studied especially the jaundice occasionally associated with chronic stasis, regards the death of the liver cells as the direct result of the congestion and as in no way referable to bacterial injury. MacCallum, accepting the arguments against the theory of pressure atrophy, is also inclined to regard stasis itself, with the consequent poor nutrition—or rather, poor oxygenation—of the cells farthest from the arterial blood supply, as the essential etiological factor.

In undertaking this investigation, we were fortunate in having at our disposal a large number of cases for study, with clinical histories, autopsy protocols, and tissue for microscopical examination, there being nearly 600 cases of all kinds at the Presbyterian Hospital and 50 cases at the Montefiore Hospital. Among these were 112 cases of well marked chronic passive congestion. In most instances the stasis was the result of some lesion in the heart or blood-vessels, but a number of other diseased states were represented—emphysema, chronic pulmonary tuberculosis, pernicious anemia, etc.—in which, as has been recognized, a condition of chronic stasis may be present.

GROSS CHANGES IN THE LIVER.

Among over 112 cases of chronic passive congestion there were 53 gross specimens. Twenty-three of these were fresh organs examined at the autopsy table; the remainder were museum specimens preserved in Kaiserling's solution. They varied considerably in size, color and consistence, but the majority were fairly typical "nutmeg" livers. The average weight of 66 specimens from adults was 1622 gm.; the extreme weights were 1010 and 2830 gm. The latter specimen was a very fatty organ. The weights of many would have been considerably greater had the blood not been allowed to drain out. The shrinkage after the vessels were cut was sometimes considerable. The smaller livers came usually from cases of long continued stasis, which showed microscopically much loss of liver substance with collapse. In the larger specimens fatty changes or extreme grades of cloudy swelling were nearly always seen. While the majority of the specimens were typically mottled organs, with distinct but often irregular lobulation on the cut surface, the gross appearance even in these varied considerably. In the same organ the picture was often very different in different parts. In general the stasis was most marked at the surface of the liver, or near the hilum, as indicated by the deep red color of these portions. Large, sunken, purplish red areas, with only small islands of gray surviving parenchyma about the portal spaces, were sometimes seen. In other parts of the same liver large, pale, elevated patches of parenchyma might be found. In the latter the lobulation was often indistinct, and such areas have been interpreted as regenerating nodules of liver tissue. (See Fig. 601, p. 839, in Aschoff's Text-book of Pathology, Vol. II, 1911.) After studying microscopically a number of such areas, we have been convinced that they do not represent large patches of regenerated liver tissue, but are simply groups of lobules in which the stasis is much less marked.

That regenerative changes do occur in chronic passive congestion is well known, but in all of our cases in which microscopic evidences of regeneration were found—mitosis, large multi-nucleated cells, asymmetrical lobules—the regenerative changes were never sufficient to form gross nodules of new liver tissue. The regeneration was insignificant as compared with the nodular hyperplasia often seen in portal cirrhosis. It may be mentioned here that regenerative changes were found only in cases of long standing, and were surprisingly rare in livers showing extensive hemorrhagic necrosis. Contrary to the common teaching we have found hyperplasia more often in middle-aged or in elderly individuals than in the young. This is probably due to the fact that examples of long-standing congestion are found more often in older people.

In nine out of the 112 cases studied, definite jaundice of the liver (and to a less degree of the other organs) was noted. It would seem probable, as Oertel has maintained, that the bile stasis in these cases was the result of a necrosis of the liver cells. It may be pointed out, however, that a microscopical study of livers shows in several of the jaundiced specimens little or no necrosis. On the other hand, widespread necrosis

was found in several in which there was no evidence of bile stasis.

Even after we had made a comparative study of our 53 specimens, it was difficult to group them on the basis of gross features. Certain extreme types were recognizable, however; for example, those showing marked central fat accumulation with mid-zonal hyperemia (Type III, described below) could be easily recognized. Also, the old, firm, collapsed organs (Type V, described on page 353). The commoner types, on the other hand, showing microscopically either marked dilatation of the sinusoids (Type I) or central hemorrhagic necrosis (Type IV, described on page 353) are difficult or impossible to distinguish.

MICROSCOPICAL CHANGES IN THE LIVER.

Two types of lesion have already been mentioned—(a) capillary dilatation, with narrowing and elongation of the liver cords (so-called pressure atrophy), and (b) central necrosis with hemorrhage. A careful study of our cases has convinced us that at least three other types—five in all—may be recognized. So many subdivisions of what is generally discussed as one lesion may not seem warranted. We have, however, convinced ourselves that clear-cut differences in the types described do exist. In going over our cases independently from time to time we rarely made any change in the grouping of a particular case. It should be pointed out, however, that pure types are not the rule, and that transitions are not infrequently encountered.

Type I. Capillary Dilatation with Atrophy of Central Cells (33 cases, or 30 per cent of the total number).—In this type of lesion the microscopical picture is that described in many of the text-books as characteristic of marked passive congestion, and it is the lesion on which was based the older idea that the liver cells in extreme stasis disappeared as the result of pressure atrophy. Certainly the dilatation of the sinusoids, with elongation of the cells (Fig. 1), does give the impression that the cells are compressed. Dilatation of the capillaries throughout the entire lobule is sometimes seen, but it is always most marked near the center of the lobule. That there is atrophy of the liver cells, it seems to us, can scarcely be questioned. The cells are distinctly smaller than normal, being sometimes reduced to mere strands. Degenerative changes, however, are not infrequently seen, and there can be no doubt that necrosis with hemorrhage does sometimes take place, as in Type IV, described below. Since this type of lesion, unassociated with degenerative or necrotic changes, is seen in less than a third of the cases of chronic passive congestion, it is obvious, as Mallory has pointed out, that undue emphasis has been placed upon it in the text-books. Furthermore, it is not the type of lesion found in extreme stasis resulting, for example, from advanced cardiac valvular disease, but is found most often in cases of moderate circulatory disturbance of long standing, as in arteriosclerosis, chronic nephritis or some debilitating disease, such as chronic pulmonary tuberculosis. Widespread dilatation of the capillaries is apparently a slow process. Severe or rapidly developing circulatory disturbance leads usually to necrosis with hemorrhage, as we shall point out later.

Type II. Central Degenerative Changes with or without Congestion (21 cases, or 18 per cent of the total number).—In this lesion (Fig. 2) the number of cells affected varies as in Type I; usually about one-half, or more, of the lobule is involved. The dividing line between healthy and degenerated liver cells is often quite sharp. The affected cells are reduced in size. The cytoplasm stains pink with eosin, and is often finely vacuolated and pigmented. Although the cells are small, the capillaries between the cell cords may not be dilated. On the contrary, they often appear narrow, apparently as the result of a sub-endothelial accumulation of fluid (edema), a condition to which Mallory and others have called attention. Although necrosis with hemorrhage is sometimes noted in places, the lesion is generally seen as a pure type. It corresponds closely to that described by Mallory as central necrosis without hemorrhage. But we have avoided the term "necrosis," because the cells are not dead, the nucleus is well preserved and stains normally, and the cell membrane is intact. Livers showing definitely necrotic cells have been placed in another group (Type IV).

This lesion was not associated with any particular disease of the circulatory system. It was found in cases of cardiac valvular disease, advanced myocardial fibrosis, chronic nephritis with cardiac failure; occasionally also in pernicious anemia and severe acute infections. In general it may be said that in cases showing this type of lesion there is either a well marked, though not extreme, disturbance in circulation, or else there is a condition of moderate stasis, complicated by acute infection.

Type III. Central Fat Accumulation with Mid-Zonal Hyperemia or Necrosis (9 cases, or 8 per cent of the total number).—The microscopic picture is very striking (Fig. 3). There is a zone of large fatty cells, with well preserved nuclei immediately surrounding the hepatic vein. The capillaries in this area are scarcely visible, as though compressed by the swollen liver cells which seem to be especially resistant. In the adjacent middle zone, however, capillaries are widely dilated, and liver cells are smaller and less fatty, giving an appearance similar to that about the center of the lobule in Type I. Not infrequently foci of necrosis are encountered with hemorrhage into the trabeculae as in Type IV. This type of lesion was mentioned by Mallory, and is thoroughly described by Heinrichsdorff, who applied to it the name "ring necrosis." Heinrichsdorff emphasizes the striking gross appearance of the liver—a tiny yellow spot, in which the hepatic vein is scarcely visible, forms the center of each lobule, and immediately surrounding it is a red zone or ring (hence the name "ring necrosis"), and outside that healthy liver parenchyma about the portal spaces. These gross characteristics were noted in all of our specimens, and served to differentiate them readily from other types. All of the nine livers in this group were found in cases of chronic rheumatic endocarditis, and nearly all were in individuals under 20 years of age (Cases 6 and 7). A larger series of cases will probably be necessary to determine whether this is a constant relationship.

Type IV. Central Necrosis, Usually Associated with Hemorrhage (33 cases, or 30 per cent of the total number).—Under the low power of the microscope the center of the lobule in typical examples of this lesion looks like a homogeneous mass of fresh blood; an occasional pigmented endothelial cell is visible (Fig. 4). Under higher magnification, fragments of necrotic liver cells, and the surviving reticular fibers, can be made out. The necrosis may involve only a narrow zone about the central vein, or may be so extensive as to leave only a few healthy liver cells at the margin of the lobule (Fig. 5). The necrosis ends abruptly, passing over into a narrow zone of fatty cells, which in turn merges into a mantle of normal cells around the portal spaces (Fig. 4). The early stage of this lesion has been well described by Mallory, who first recognized the picture as a true necrosis with hemorrhage into the trabecular spaces. In the majority of cases liver cells have completely disappeared, but we were fortunate in finding two in which the necrosis was very recent, and the bodies of the dead cells still remained more or less intact, with little hemorrhage. The cases throw light on the etiology of the lesion about which there has been a good deal of dispute. Each of the patients had been suffering for a considerable time from "heart trouble," with mild symptoms of circulatory failure. One patient (Case 9, see protocol) developed suddenly, seven days before death, signs of cardiac failure, which increased progressively until death. The other, an elderly man, who was also living a comfortable life, collapsed suddenly 11 days before death. In each of these cases arteriosclerosis of the coronaries was found at autopsy, with recent thrombosis of one of the larger branches. In neither was there a terminal complicating infection. These two cases afford definite proof that necrosis of liver cells may be caused by stasis alone. This conclusion has been more firmly established by a tabulation of our entire series of cases with regard to the existence of terminal or recent infections. Briefly stated, it was found that the percentage of infections, including pneumonia, pleurisy, peritonitis, meningitis and sepsis, was practically the same in Type I, where no necrosis was observed, as in Type IV, hemorrhagic necrosis. Ten cases of bacteremia, staphylococcic, streptococcic and pneumococcic, were likewise about equally distributed among the several types. It should be mentioned, however, that in all the cases of streptococcic sepsis necrotic lesions were found, though in one instance (Case 5, see protocol) they were focal in distribution.

In general it may be stated that the only constant etiological factor in cases of hemorrhagic necrosis is a severe circulatory disturbance. This statement is based on a careful review of clinical and autopsy findings in our large series of cases. The cause of the circulatory disturbance was in every case very evident. The majority showed advanced cardiac valvular disease, involving usually several valves. A few showed extreme myocardial fibrosis. The most extensive destruction of liver tissue (Case 8, Fig. 5) was seen in a case of aortic aneurism with rupture into the superior vena cava, resulting in the most extreme disturbance in circulation.

Type V. Collapse Fibrosis; So-Called "Cardiac Cirrhosis" (16 cases, or 14 per cent of the total number).—In this type of lesion each central vein is surrounded by a loose non-cellular connective tissue in which a quantity of blood pigment is found (Figs. 6 and 7). We have observed this lesion only in chronic cardiac cases, the majority of long standing, with a history of periodic attacks of decompensation, followed by improvement (Cases 11 and 12).

It is evident that the liver cells must have disappeared either by a process of atrophy or of necrosis. The presence of much free and intracellular blood pigment, and the demonstration in many sections of transitions from Type IV, have led us to conclude that collapse fibrosis represents usually the terminal stage of central hemorrhagic necrosis, as Mallory has suggested. The connective tissue, in most cases at least, seems to be merely a condensation of the pre-existing fibrillar connective-tissue framework in the affected portion of the lobule. Herxheimer, however, in a recent paper, has concluded that the reticular fibers (Gitterfasern) are considerably increased in advanced stasis, but his descriptions and illustrations are not altogether convincing. He does not appear to have taken into consideration the collapsed state of the lobule which follows extensive central necrosis. Two of our 16 cases (less than 2 per cent of the 112 cases of chronic passive congestion) seem to show an active proliferation of connective tissue (Case 11, see protocol). The change is not diffuse, being most pronounced at the surface of the organ. The microscopic picture is strikingly different from that of Laennec cirrhosis, in that the connective-tissue increase is confined to the region about the center of the lobule. In some places the central veins are connected by connective-tissue strands, encapsulated lobules of liver parenchyma being thus formed of which the bile ducts are the centers. In no case did we find evidence of cirrhosis of the ordinary nodular type developing as the result of chronic passive congestion. In rare cases, when the two lesions were seen in the same liver, the cirrhosis was obviously primary.

CONCLUSIONS.

1. The microscopic picture of the liver in chronic passive congestion is very varied. At least five types of lesion may be recognized:

- (a) Capillary dilatation with atrophy of the cells toward the center of the lobule (Fig. 1);
- (b) central degeneration with or without capillary dilatation (Fig. 2);
- (c) marked fat accumulation in the cells about the hepatic veins with mid-zonal hyperemia (Fig. 3);
- (d) central necrosis with hemorrhage (Figs. 4 and 5);
- (e) collapse fibrosis (Figs. 6 and 7).

2. The type of lesion present at autopsy is determined chiefly by the degree of circulatory disturbance and its duration. Long-continued stasis of slight or moderate grade leads to capillary dilatation with progressive atrophy of the liver cells (Type I). Degenerative changes in the liver cells (Type II) are due either to stasis of more marked degree, or to moderate congestion in conjunction with infection. Extreme stasis results in central necrosis with hemorrhage (Type IV), which passes over into collapse fibrosis (Type V) if death be

delayed long enough. The latter lesion also results occasionally from an extreme degree of atrophy (Type I). Central fat accumulation with hyperemia of the intermediate zone is commonly associated with chronic rheumatic endocarditis in young individuals.

3. The necrosis of the liver cells in chronic passive congestion is the effect of stasis alone, leading to asphyxia of the cells farthest removed from their arterial blood supply. Infection plays a minor part in causing a definite necrosis, although it probably contributes to the production of degenerative changes in the liver cells (Type II). Very extensive necrosis is not infrequently seen in cases of extreme stasis unassociated with infection.

4. Active regeneration of liver tissue is not regularly seen in chronic passive congestion. It is conspicuously absent in those cases of hemorrhagic necrosis where the loss of liver tissue is greatest. It is observed most often in cases of circulatory disturbance of long standing.

5. Chronic passive congestion never leads to the development of cirrhosis of the usual portal or nodular type. Collapse fibrosis, not infrequently seen, is not a true cirrhosis, but a condensation of the reticular fibers where the liver cells have disappeared. In only 2 out of 112 cases of chronic passive congestion was an active new growth of connective tissue observed. In these the change was limited to certain parts of the liver, with an involvement of the central portion of the lobule only, producing a picture very different from that of portal cirrhosis.

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PROTOCOLS.

Type I.

CASE 1.—Male, aged 46. Hay fever and asthma 13 years, digestive disturbances 2 years. Later symptoms: nocturnal dyspnea, headache, weakness, edema of legs and face. Treated in the hospital 7 weeks, where he developed furunculosis and staphylococcus bacteremia.

Anatomical Diagnosis.—Arteriosclerosis of smaller vessels; arteriosclerotic contracted kidney; emphysema; hypertrophy and dilatation of heart (weight, 710 gm.); staphylococcus abscesses in lungs and kidneys; bronchopneumonia; chronic passive congestion of organs.

Liver.—Enlarged, mottled, uniform distinct lobulation. *Micros.*—Moderate capillary dilatation, with atrophy of liver cells of inner half of lobule. No necrosis, and no degenerative changes except cloudy swelling.

CASE 2.—Male, aged 58. The chief symptoms were weakness, dyspnea, swelling of the feet and legs, cough. In hospital 4 days.

Anatomical Diagnosis.—Generalized arteriosclerosis, with involvement of coronaries; myocardial fibrosis; arteriosclerotic atrophy of kidneys (moderate); hypertrophy of heart (weight, 540 gm.); bilateral hydrothorax; chronic passive congestion of viscera.

Liver.—Enlarged, mottled, distinct lobulation. *Micros.*—Extreme capillary dilatation, with atrophy of liver cells near the hepatic veins.

CASE 3.—Male, aged 59. Dyspnea on exertion; orthopnea; polyuria. In hospital three times during the last year of life; improved at first by rest in bed; during the last admission the edema became very marked.

Anatomical Diagnosis.—Chronic nephritis (combined arteriosclerotic and inflammatory); hypertrophy and dilatation of heart (weight, 850 gm.); edema of lungs; bilateral hydrothorax; chronic pancreatitis; chronic passive congestion of viscera.

Liver.—Typical "nutmeg" type; much blood flowed out when the vessels were cut. *Micros.* (Fig. 1).—Extreme capillary dilatation; atrophy of liver cells of the inner two-thirds of lobule.

Type II.

CASE 4.—Male, aged 42. Rheumatism 14 years ago; chief symptoms, precordial pain upon exertion and poor appetite. In hospital 1 day. Corrigan and capillary pulse; rapid respiration; chill; temperature 102.6° F.

Anatomical Diagnosis.—Syphilitic aortitis; aortic stenosis; hypertrophy of left ventricle (slight); focal degeneration of heart muscle; emphysema; acute fibrino-purulent pericarditis; chronic passive congestion of organs.

Liver.—Weight 2100 gm. Uniform distinct lobulation; periphery of lobule yellowish brown, center red and slightly sunken. *Micros.*—Cells in central half of lobule are reduced in size, cytoplasm vacuolated; nuclei well preserved; slight dilatation of capillaries. Peripheral cells show cloudy swelling.

CASE 5.—Female, aged 36. Rheumatic fever many years ago; weakness, dyspnea on exertion 4 years; swelling of legs, several

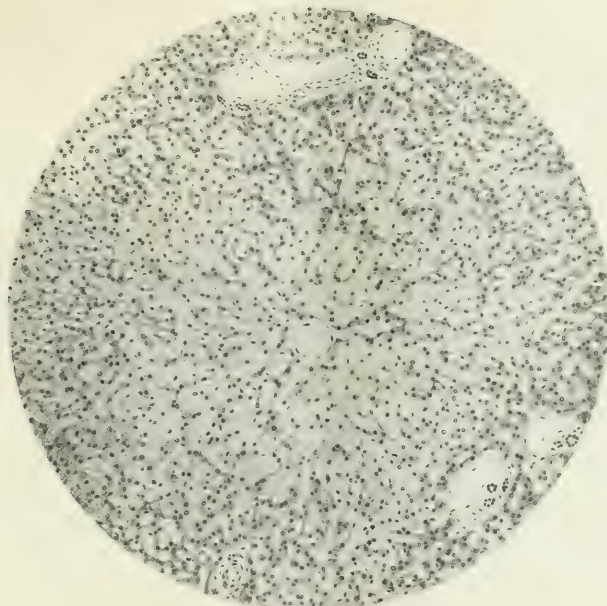


FIG. 1.

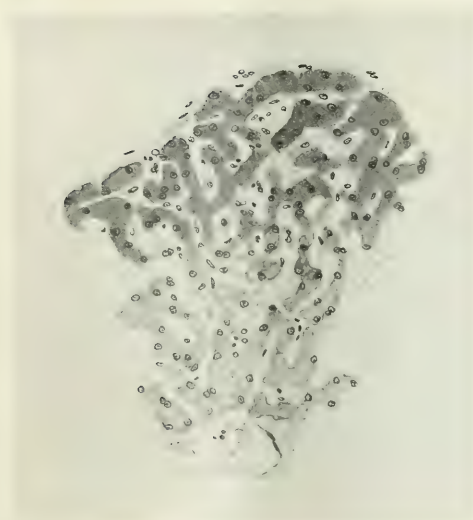


FIG. 2.

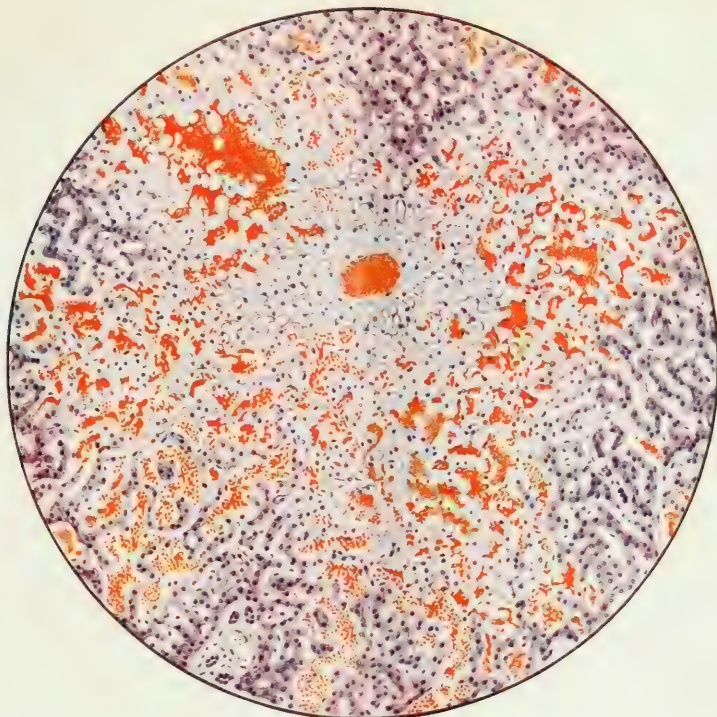


FIG. 3.

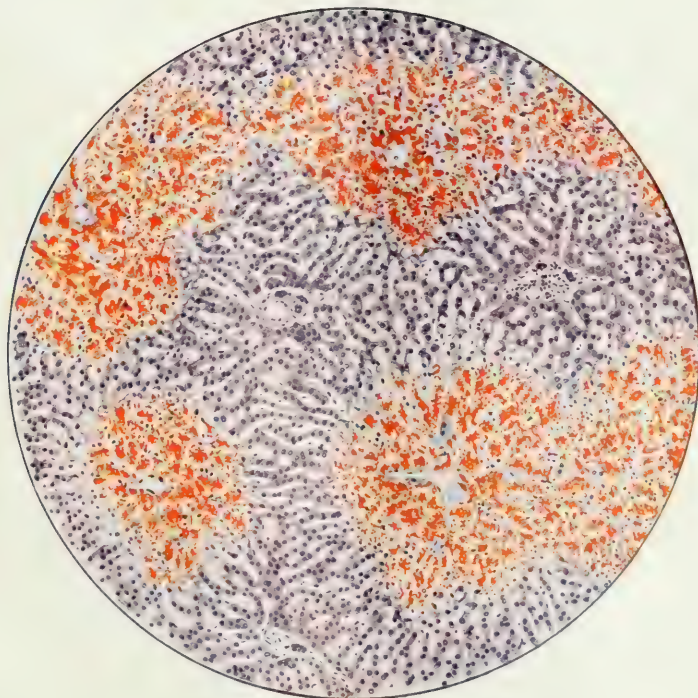


FIG. 4.

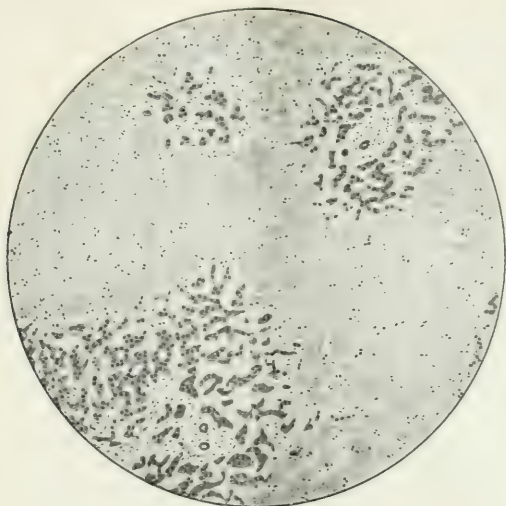


FIG. 5.

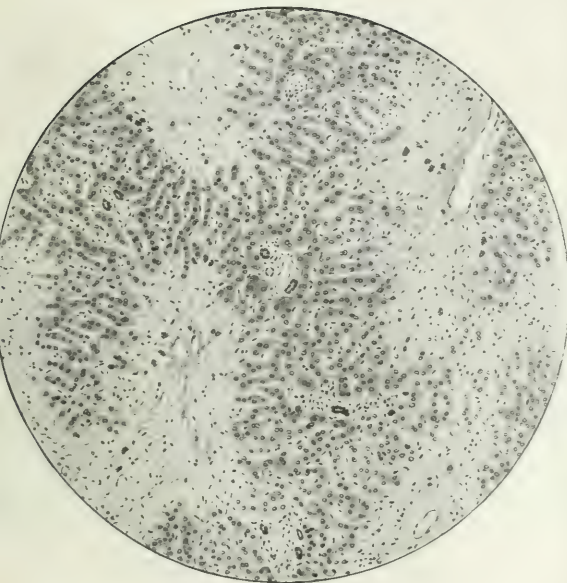


FIG. 6.

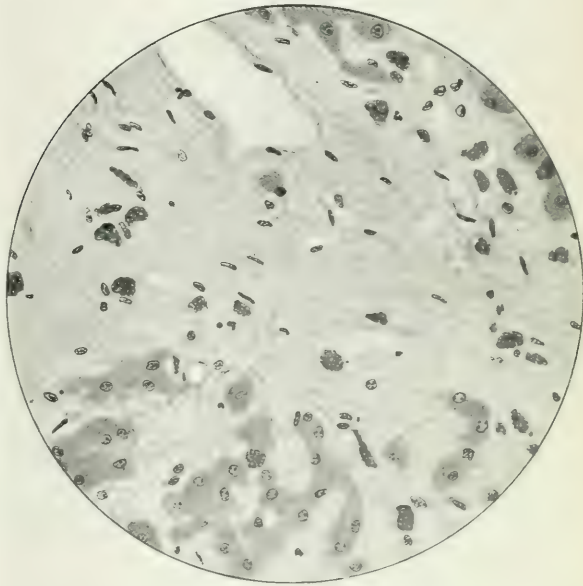


FIG. 7.

months. In hospital 6 weeks with chilly sensations, fever, weakness. *Streptococcus viridans* obtained in blood culture during life; circulatory disturbance not so pronounced as toxæmia.

Anatomical Diagnosis.—Acute and chronic endocarditis, involving mitral, aortic and tricuspid valves, and with vegetations on wall of auricle; acute myocarditis; hypertrophy of heart (weight, 580 gm.); œdema of lungs and extremities; acute and chronic glomerular nephritis; infarcts of kidneys; petechiæ in skin and mucous membranes; chronic passive congestion of organs.

Liver.—Weight, 1650 gm. Lobules small; uniform size, depressed red centers. *Micros.* (Fig. 2).—Cells in central half of lobule small, vacuolated and pigmented; vessels not dilated; occasional focal hemorrhages in mid-zonal portion of lobule.

Type III.

CASE 6.—Male, aged 10. Rheumatic fever 5 months ago, followed by swelling of ankles. In hospital 1 month. Described as typical heart case, with increasing œdema. Temperature normal, rising to 100° F. once.

Anatomical Diagnosis.—Chronic endocarditis, mitral and aortic; hypertrophy and dilatation of heart (weight, 270 gm.); chronic myocarditis; hydrothorax and ascites; petechiæ in skin.

Liver.—Somewhat enlarged; centers of lobules bright yellow, with central veins visible as small red points; a deep red ring surrounds the yellow; in places the red areas are extensive. *Micros.* (Fig. 3).—Marked fat accumulation in central cells; mid-zonal hyperæmia with necrosis in places.

CASE 7.—Male, aged 17. Acute rheumatic fever 7½ months before death, followed by dyspnea, cyanosis and weakness. In hospital 7 months, where he developed a suppurative pleurisy, with intermittent fever, leucocytosis and cough.

Anatomical Diagnosis.—Chronic rheumatic endocarditis, mitral and aortic; acute rheumatic myocarditis; hypertrophy of heart (weight, 700 gm.); adherent pericardium; suppurative pleurisy; chronic pulmonary tuberculosis; chronic passive congestion of organs.

Liver.—Weight, 1200 gm. Irregularly mottled; central vein surrounded by yellow zone; red streaks and patches between center and periphery. *Micros.*—Few normal liver cells about portal spaces, central cells very fatty; mid-zonal hyperæmia.

Type IV.

CASE 8.—Female, aged 33. Shortness of breath 2½ years; cyanosis; difficulty in swallowing; swelling of face and neck 6 months. In hospital 14 times during the last year of life. Chief symptoms referable to pressure of aortic aneurism and extreme disturbance in circulation; never septic.

Anatomical Diagnosis.—Aneurism of ascending aorta perforating superior vena cava; aortic stenosis; fibrino-purulent pleurisy; jaundice; extreme circulatory stasis, most marked in liver.

Liver.—Weight, 1850 gm. Purplish red in color, with only small islands of yellowish-grey parenchyma surrounding the portal vessels. *Micros.* (Fig. 5).—Extreme hemorrhagic necrosis affecting the entire lobule in places.

CASE 9.—Male, aged 44. Periodic attacks of dyspnea and faintness 18 years. One week before death he was seized with a sudden severe pain in the precordium, becoming intermittent in character. In the hospital he showed marked cyanosis; air hunger; tenderness in the epigastrium; enlarged liver.

Anatomical Diagnosis.—Generalized arteriosclerosis, involving the coronaries; thrombosis of the descending branch of the left coronary artery with infarction of the left ventricular wall; thrombi in the left ventricle and auricle; acute fibrinous pericarditis; arteriosclerotic atrophy of the kidney (slight); hypertrophy of the heart (weight, 675 gm.); chronic passive congestion of organs.

Liver.—Weight, 1510 gm. Firm, nutmeg color; centers of lobules deep red, depressed. *Micros.*—Recent necrosis of liver cells in the central two-thirds of the lobule; cell form preserved in most places, pyknosis and fragmentation of nuclei; beginning hemorrhage into the trabecular spaces in places.

CASE 10.—Male, aged 23. Acute rheumatism 3 years before death. Swelling of feet and abdomen 3 months; cough, orthopnea, cyanosis. In hospital 6 weeks; pitting œdema of legs, ascites; pulsating liver. Temperature normal except 1 day. Leucocytes 10,300; polynuclears, 70 per cent; blood pressure, 104/72.

Anatomical Diagnosis.—Chronic rheumatic endocarditis and acute vegetative endocarditis, involving mitral, aortic and tricuspid valves; adherent pericardium; calcification of heart muscle (focal, microscopic); calcification of diaphragm; hypertrophy of heart (weight, 850 gm.); œdema of lungs; ascites; chronic passive congestion of viscera.

Liver.—Weight, 2000 gm. Strikingly mottled; light yellow areas along afferent blood-vessels on a bluish red background. *Micros.* (Fig. 4).—The inner half to three-fourths of each lobule shows a mass of blood with no surviving liver cells, surrounded by a narrow zone of fatty liver cells. Peripheral cells, normal.

Type V.

CASE 11.—Male, aged 45. In the hospital twice suffering from dyspnea on exertion, nausea, vomiting, gnawing abdominal pain; excessive phlegm in throat; enlarged heart and liver; hemorrhoids.

Anatomical Diagnosis.—Myocardial fibrosis with arteriosclerosis of the coronary vessels; hypertrophy and dilatation of the heart (weight, 580 gm.); infarcts in the lung; thrombi in the heart; lobular pneumonia; abscesses in the lung; chronic passive congestion of organs.

Liver.—Weight, 1470 gm. Very firm and tough; distinct lobulation, centers of lobules depressed; peripheries pale. *Micros.*—Zone of actively proliferating connective tissue around each central vein; change found chiefly near surface of liver.

CASE 12.—Male, aged 55. Chief symptoms, dyspnea, orthopnea, swelling of abdomen and legs, scanty urine, 7 months' duration. In the hospital 7 weeks. Liver enlarged, tender and pulsating; frequent tapplings of right chest; no history of infection.

Anatomical Diagnosis.—Arteriosclerosis of coronaries; myocardial fibrosis; hypertrophy and dilatation of heart (weight, 575 gm.); thrombi in auricles and ventricles; lobular pneumonia; œdema of lungs; hydrothorax; chronic passive congestion of organs.

Liver.—Weight, 1400 gm. Distinct lobulation; border of lobule elevated, intralobular tissue red and sunken. *Micros.* (Figs. 6 and 7).—Collapsed areas about central veins, deposition of much pigment. In some lobules typical hemorrhagic necrosis, and transitions into "collapse fibrosis."

ILLUSTRATIONS.

Fig. 1.—Chronic passive congestion, Type I. Marked dilatation of capillaries, especially in central zone; extreme atrophy of liver cells; no necrosis or hemorrhage. Case of nephritis, cardiac hypertrophy and dilatation. (See protocol, Case 3.)

Fig. 2.—Chronic passive congestion, Type II. Degenerative changes in cells of inner half of lobule. Affected cells are reduced in size; nuclei normal; cytoplasm vacuolated and pink-staining. No necrosis. Case of subacute bacterial and chronic endocarditis of mitral and aortic valves. (See protocol, Case 5.)

Fig. 3.—Chronic passive congestion, Type III. Cells about hepatic vein, very fatty; dilatation of capillaries in intermediate zone with focal hemorrhages. Case of chronic rheumatic endocarditis of mitral and aortic valves. (See protocol, Case 6.)

Fig. 4.—Chronic passive congestion, Type IV. Necrosis of cells in inner half of lobule with hemorrhage into the trabecular spaces.

Narrow zone of fatty cells surrounding necrotic areas. Peripheral cells normal. Case of chronic rheumatic endocarditis involving mitral, tricuspid and aortic valves. (See protocol, Case 10.)

Fig. 5.—Chronic passive congestion, Type IV. Extensive central necrosis with hemorrhage involving entire lobule in places. Case of aortic aneurism perforating superior vena cava. Extreme circulatory disturbance. (See protocol, Case 8.)

Fig. 6.—Chronic passive congestion, Type V. Disappearance of

liver cells in central portion of lobule with collapse fibrosis and pigment deposition. No active proliferation of connective tissue. Peripheral cells are large and some show two nuclei. Case of arteriosclerosis of coronary vessels with advanced myocardial fibrosis. (See protocol, Case 12.)

Fig. 7.—Chronic passive congestion, Type V. Higher magnification of Fig. 6, showing condensation of reticulum about hepatic veins and phagocytosis of pigment by endothelial cells.

THE REACTION OF THE SPLEEN IN ACUTE INFECTIONS.

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The reactions of the spleen in the commoner acute infections merit more attention than that given them by the simple designation, acute splenic tumor. A complete understanding of the processes would go far in clearing up the obscure functions of the spleen, would do much in demonstrating the pathological physiology of many wandering cells of the body, and possibly point the way to a clearer appreciation of several pathological processes. But such an understanding is dependent upon a knowledge of the histology of the spleen and the various cells found there, and such knowledge of this as is available is not complete or definitely proven. But some points are known, and others have been suggested, and acute splenic tumor studied in the light of these establishes some of the suggestions made, and at least indicates a possible answer to some of the above questions. It has been the object of this study to interpret the histology of acute splenic tumor, as seen at autopsy, on the basis of what is already known of the cells in the spleen, and to control these interpretations by experimentally induced acute splenic tumor in animals under various conditions.

THE HISTOLOGY OF THE SPLEEN.

It here becomes necessary to discuss briefly what is known, and what has further been suggested, in regard to the histology of the spleen. The structure of the spleen as worked out by Weidenreich¹ and Mollier² will not be discussed in detail, as it is readily available in the original articles of these authors, and in various text-books of histology and pathology. It will suffice to restate from these authors that the Malpighian corpuscles are collars of lymphoid tissue around the arterioles of the spleen, arterioles that eventually empty into a wide network of venules in the pulp lined with endothelial cells; and between these venules, and for the most part passing freely in and out of them, lie cells of diverse form—the pulp cells. The Malpighian corpuscles can be considered as lymphoid nodules and, except for the occasional enlargement and proliferation of some of the large cells in the center,³ seen in acute infections, especially in children (in all probability merely part of a general hyperplasia of the lymphopoietic tissue of the body), take no part in the processes resulting in acute splenic tumor. The pulp cells, however, are intimately con-

cerned in the histological picture of acute splenic tumor, and demand further inquiry into their nature and function.

There has been much speculation but little proven about the different forms of mononuclear cells in the splenic pulp, and, although it can be stated with some degree of certainty that there are several definitely established types of cells present, a differentiation between all of them with the usual stains is not possible in tissue sections. True small lymphocytes may be recognized in any preparation, vitally staining histogenous macrophages are demonstrable by the vital stains, and myeloid cells are proven by the oxydase reaction. Yet there are still other cells for which definite diagnostic criteria are not available. Some of these pulp cells are intimately related to the reticular elements, others seem to be entirely independent of them; and in most routine tissue sections many cells that appear to be in the pulp probably in reality represent endothelium lining venous sinuses. And the mere recognition of endothelial cells as such would not end the problem as far as they are concerned; for they take an active part in the pathologic histology of acute splenic tumor, and are intimately related in some obscure manner to other mononuclear cells of the pulp. They can, for instance, become swollen and act as phagocytes, and their intimate relation, and perhaps transition, to the reticulum cells suggest that they may become free, wandering together with the other pulp cells. Mallory⁴ recognized the phagocytic properties of these endothelial cells in typhoid fever, and was so convinced that they become free and subserve functions other than that of lining venous sinuses, that he speaks of many mononuclear wandering cells of the tissues and blood as endothelial leucocytes.⁵ Marchand⁶ likewise maintains they can become free, go over into the blood and become large mononuclear wandering cells; and the pathological picture in Gaucher's disease,⁷ in which these cells, or closely related forms, are concerned in the pathological process with vitally staining reticulum cells,⁸ makes it certain that the endothelium lining venous sinuses in the spleen must receive more attention in the histological study of acute splenic tumor than would be accorded them as mere lining pavement cells. The cells mentioned above with which the sinus endothelium appears so closely related, the so-called reticulo-endothelial cells—vitally staining histogenous macro-

phages—make up a widely distributed group of cells in the body with fairly well defined function and diverse morphology.⁹ These are the principal cells concerned in the phagocytosis in typhoid fever noted by Mallory and named by him endothelial leucocytes, and in the pathological picture of Gaucher's disease.⁸ Only after previous careful study with the vital stains can they be recognized on morphological grounds alone in the spleen by the usual stains, and then with no great certainty; but in vitally stained animals they can be demonstrated throughout the pulp and in the Malpighian corpuscles in intimate association with the reticulum.* The relation of these cells to other wandering cells of the body is obscure, but that they are active wandering cells is admitted by all observers, and some maintain they are intimately concerned with the mononuclear wandering cells of the blood.^{5, 6, 10} Pappenheim,¹¹ although admitting such a relation for cells of this group elsewhere in the body, maintains that those in the spleen—which he names splenocytes—are fixed cells. Whatever their genetic relation may be, by means of the vital stain and oxydase reaction they can be differentiated from adult lymphoid and myeloid cells,¹² and study of their reaction in acute splenic tumors brings further proof that such a differentiation is justifiable. That, aside from the polymorphonuclear cells of the circulating blood present, myeloid or at least myelopotent cells are found in the spleen pulp seems likely from the myeloid metaplasia seen there under some conditions, and can be beautifully demonstrated by means of the oxydase reaction in frozen sections of the spleen.¹³ By this method perhaps one-third or more of the cells of the pulp are seen to be myeloid, and the follicles to be entirely free of them. Of course many adult polymorphonuclear and oxydase mononuclear (so-called transitional) cells are present in the blood of the venous sinuses and pulp, but these do not account for all the oxydase cells seen there, and force one to the conclusion, in agreement with Paramusoff,¹⁴ that even in the normal spleen there are certain mononuclear myelopotent immature cells that do not go over into the circulating blood. In addition to the readily recognized true lymphocytes, the vitally staining histogenous and the sinus endothelial cells, and the oxydase cells, there are yet others in the splenic pulp that morphologically cannot be distinguished from some of the cells identified as above outlined, but which react differently to these biological reactions. They are probably lymphoid in relation and many may be some type of plasma cell;^{15, 16} and it seems certain that many of them are examples of the non-oxydase mononuclear cells of the blood, not filtered out there as Pappenheim would have it,¹⁷ but formed in the spleen and by it contributed to the large mononuclear group of blood

* It seems evident that the Malpighian corpuscles are merely lymphoid nodules, and that most of the large cells at the center are immature fixed cells that give rise to the true small lymphocytes. The presence also of a few vitally staining histogenous macrophages as reticulum cells in the same areas, and the different functional activity which they manifest under some conditions, probably have given rise to most of the scepticism in regard to the lymphoblastic character of most of the large fixed cells in the center of the follicles.

cells.¹⁷ Furthermore, it would seem that the spleen is a more or less active erythropoietic organ,^{18, 19, 20} so that it cannot be denied that some of these cells are fixed mother-cells of the erythrocytes, although the rare occurrence of normoblasts in the spleen normally makes this hard to believe. However, whatever the remote relations existing between cells of the splenic pulp are, it may be definitely stated that, with the exception of its vitally staining histogenous macrophages—and the endothelial cells—they are fundamentally hæmatopoietic in character. As part of the evidence in favor of this statement may here be cited the reaction of the splenic pulp to benzol poisoning. After sufficiently prolonged benzol administration the leucopoietic tissue is destroyed and the bone-marrow rendered aplastic. The splenic pulp is affected in the same manner as the bone-marrow, so that in heavily poisoned animals the spleen is represented by a collapsed bit of tissue made up only of reticulum, reticulum cells and endothelium.²¹ And it may further be stated that the splenic pulp cells can be divided, on biological grounds, into three groups:^{12, 22} (1) Vitally staining and sinus endothelial cells; (2) oxydase-containing cells; (3) non-oxydase mononuclear cells and true lymphocytes. It is on the basis of this classification that acute splenic tumor has been studied.

STUDY OF AUTOPSY MATERIAL.

In the gross, two types of acute splenic tumor may be recognized which, from their most obvious characteristic, will here be spoken of as red and gray, a designation already in common

RED.	GRAY.
<p>TYPHOID AND PARATYPHOID FEVER, ETC.</p> <p>The largest acute splenic tumors are of this type. They may, however, be quite small. Those studied varied in weight from 120 to 950 gm., with an average for 21 specimens of 387 gm.</p> <p>The organ is very soft and diffuent; it does not maintain its shape.</p> <p>The capsule is always tense.</p> <p>The pulp bulges markedly above the level of the cut surface, and is very moist.</p> <p>Dark red-brown color, homogeneous.</p> <p>The trabeculae are completely obscured; they become very prominent after the cut surface has been scraped.</p> <p>The spleen may collapse markedly after section of the vessels.</p>	<p>PNEUMONIA, SEPTICEMIA, ENDOCARDITIS, ETC.</p> <p>The spleen may be very large, but the increase in size is commonly only moderate. Those studied varied in weight from 100 to 750 gm., with an average for 29 specimens of 324 gm.</p> <p>It is soft but not diffuent as in the red type; the organ maintains its shape.</p> <p>The capsule is never wrinkled, but is often not tense.</p> <p>The pulp bulges moderately above the level of the cut surface, and is not so moist as in the red type.</p> <p>Dirty red-gray color; often mottled dark-red and gray.</p> <p>The trabeculae are not completely obscured, and occasionally seem more prominent than usual. They do not become so much more prominent, as in the red type when the cut surface is scraped.</p> <p>The spleen shows practically no collapse after section of the vessels.</p>

use. All acute splenic tumors studied have been found to belong to one or the other of these two types, and only very rarely is an example encountered which cannot readily be placed in its proper group on gross inspection alone. Named from the most easily appreciated difference, these two types of acute splenic tumor have other individual characteristics that are very constant in occurrence, those of the red practically never seen in the gray, and *vice versa*. Similarly, their clinical association is just as constant, the red, and only the red type, seen in typhoid fever and typhoid group infections, and practically in no other condition; the gray, and always the gray type, wider in its distribution, occurring in pneumonia, bacterial endocarditis and other staphylococcus and streptococcus infections, etc. The gross differences between these two kinds of acute splenic tumor may be conveniently brought out by tabulation as shown on the preceding page.

Under the microscope there are similarly two characteristic pictures in acute splenic tumor, the line of division running parallel to that of the classification based on gross appearances. Some sections are encountered that are not typical of either, and present difficulties in the interpretation of the histological picture; but most of them can be properly placed without hesitation.

1. *Red Acute Splenic Tumor* (Fig. 1).—For a description of the histology of this type of acute splenic tumor little can be added to that of Mallory for the changes in the spleen in typhoid fever:⁴

As a rule the lymph nodules of the spleen do not show any marked change in typhoid fever. In certain cases, however, some or all of the nodules show to a greater or less extent the same formation of phagocytic cells from the endothelial cells of the reticulum that is found in the lymphoid tissue of the intestine.

The most marked changes of the spleen are those found in the blood-vessels and spaces of the pulp. They are much dilated and filled with large phagocytic cells containing principally red blood globules usually in very large numbers, but also lymphoid and plasma cells and polymorphonuclear leucocytes. These phagocytic cells are derived chiefly or entirely by proliferation and desquamation from the endothelial cells lining the vessels. Occasionally mitosis takes place in the cells lying free in the blood. Sometimes the blood-vessels and spaces become occluded by masses of these large cells, which degenerate and become bound together by a meshwork of fibrin.

Besides this general proliferative process we get, as in the intestine, numerous plasma cells in the veins and in the splenic pulp. Many of them show ameboid shapes and not infrequently mitosis. In some of the splenic veins, especially the larger ones, the lining endothelium is lifted up by masses of large phagocytic cells, and of lymphoid and plasma cells. In places these cells degenerate and fibrin forms between and around them.

The great amount of blood in the sinuses and pulp and the striking proliferation of the reticular and endothelial cells mentioned by Mallory are to be observed as the two most characteristic features of this type of acute splenic tumor. The great scarcity and almost complete absence in many sections of polymorphonuclear cells and the diminution of pulp cells of all types, should be emphasized. That some mononuclear cells of special morphology, considered by Mallory to be plasma cells, are present in increased numbers must be ad-

mitted. Although we realize that no definite statement of their true character is possible, their intimate relation with the reticular and endothelial elements, which might even be interpreted as proliferation from them, makes it seem possible that many are in reality changed forms of endothelial cells or the vitally staining histogenous macrophages. The group of vitally staining cells includes some showing diverse morphological characteristics,⁹ and some have many points of resemblance to true plasma cells.¹²

2. *Gray Acute Splenic Tumor* (Fig. 2).—In contradistinction to the red type, the gray acute splenic tumor is characterized by the cellularity of the tissue; and although an excess of blood is present, it is for the most part confined to the venous sinuses. The endothelial cells lining the venous sinuses are little, if at all, swollen and never show proliferation. The cells of the reticulum are often somewhat swollen, but are not increased in number, and show practically no proliferation. One of these, containing red blood cells and tissue debris, is occasionally encountered, but phagocytosis is not common. The Malpighian corpuscles in some specimens are large, and in others small; but they never show any undue prominence of the large fixed cells at the center of the follicle, such as is to be observed in the red type, or fragmentation of the true small lymphocytes around the periphery. The cellularity of the sections is dependent on the number of cells in the pulp which are present in more than normal proportions in spite of the active congestion of the organ, manifested by the distention of the venous sinuses with blood. Many of these cells are polymorphonuclears, many have the morphological characteristics of normal oxydase mononuclears and myelocytes. Among the great numbers of pulp cells seen in gray acute splenic tumor, these cells are shown by the oxydase reaction to be more than proportionately increased, although this proportionate increase of the oxydase-containing cells is always slight and never striking. There are also a few nucleated red blood cells in each specimen, never numerous but always to be found if searched for diligently enough. The other cells are lymphocytes, which perhaps are increased in number but certainly not proportionately, and the obscure non-vital staining, non-oxydase mononuclear cells of the normal pulp mentioned above. The predominance of the cells resembling plasma cells, which commonly occurs in the red, is not seen in this type. In the gray type the trabeculae seem to be stouter and more prominent than in the red acute splenic tumors.

Thus it is apparent from the study of acute splenic tumors as seen at autopsy, that there are two distinct types, each of which has certain distinctive characteristics and both an excess of blood, show in common active congestion. The size of the spleen is, entirely in the red and in large part in the gray acute splenic tumors, dependent upon the amount of congestion, sections from the larger spleens showing regularly more blood than those from the smaller. The softer consistence and red color of the red type are a result of the excess of blood present, the somewhat firmer consistence and gray color of the gray type are due to its smaller amount of blood and the

greater abundance of pulp cells. The red acute splenic tumors are characterized by a diminution in the pulp cells, particularly the myeloid elements, proliferation of the vitally staining reticulum and the endothelial macrophages, and an active phagocytosis; whereas in the gray type we have an increase in the pulp cells, especially the myeloid elements, absence of increase in the macrophages, and only a slight grade of phagocytosis. It is more than incidental that typhoid fever, a clinical condition associated with hypoleucocytosis and showing pathologically active phagocytosis with proliferation of the macrophages in the lymph glands, lymph follicles of the intestine, etc.,⁴ together with a diminution of the leucopoietic function of the bone-marrow,²³ should show in the spleen the changes outlined above; and that those clinical conditions associated with a hyperleucocytosis, hyperactivity of the bone-marrow²³ and practically no phagocytosis, present the reaction in the spleen already described for them. On the basis of these studies it seems safe to postulate a relation between the reactions in the spleen in acute infections and their characteristic general manifestations; to say that, in addition to the active congestion present in each, the histological picture seen in the red type of acute splenic tumor is part of the general associated leucopoietic, especially myelopoietic, inhibition, with consequent hyperplasia of the histogenous macrophages; and that that of the gray type is part of a hyperplasia of the leucopoietic, especially the myelopoietic, tissues of the body related to the hyperleucocytosis present.

To afford experimental evidence for these hypotheses the following experiments were undertaken, in which an attempt was made to induce acute splenic tumor of both the red and the gray types in animals under various conditions.

EXPERIMENTAL PART.

TECHNIQUE.

Rabbits were used in all the experiments. Except for the presence of oxyphile with relative decrease in neutrophile polymorphonuclears, the cells in these animals are similar to those in the human subject. The histology of the rabbit spleen is essentially like that of the human spleen, except that the Malpighian corpuscles are relatively much larger, the venous sinuses stand out more prominently, and the pulp is relatively less abundant. The spleen of the rabbit seems to be very sensitive to infections, for animals suffering from no more severe infection than early "snuffles" regularly present some evidence of acute splenic tumor. Rabbits cannot be killed with strains of the human typhoid organisms, but with them reactions can be produced in the spleen without the animal even showing evidence of being ill. The most satisfactory reaction to organisms of this type, however, were obtained by the intravenous inoculation of 1/15 to 1/50 of a 24-hour agar slant culture of an organism isolated from an epidemic of rat typhoid, studied and identified by Pappenheimer²⁴ as identical with *B. enteritidis* (Gaertner). To produce gray acute splenic tumor pneumonia was induced by the intrabronchial inoculation after the method of Meltzer²⁵ of 8 cc. of a 24-hour neutral broth culture of several different

stains of attenuated pneumococci and streptococci; and to produce a cellular pneumonic exudate without bacillary intoxication, 8 cc. of a 33 per cent solution of sterile egg-yolk in neutral broth, as used by Kline and Meltzer,²⁶ were similarly injected. To render animals aleukemic, benzol was administered subcutaneously, 1 cc. per kilogram of body weight in an equal amount of olive oil, as used by Selling.²¹ In these benzol experiments most of the observations were made on animals not entirely aleukemic; for in such animals the resistance is so much lowered that inoculation with any pathogenic organism kills before pathological changes have had time to take place.

1. ACUTE SPLENIC TUMOR IN RABBITS.

These experimental acute splenic tumors, although induced by the same or closely related organisms that give rise on the one hand to the red and on the other to the gray type in human subjects, in rabbits cannot be divided into these two classes on the gross appearances alone. The difference in size encountered was considerable, depending, in large part it seems, on the duration of the pathological process, since the animals that were heavily inoculated and died early did not show as large tumors as those that received smaller doses and survived for a relatively long time. As in human acute splenic tumor, the size depended almost entirely on the amount of active congestion present. The spleen was always soft, rarely diffuent, and the edges markedly rounded. On section the pulp bulged far beyond the level of the cut, and much material could be scraped from the surface, although in none of these acute splenic tumors (of rabbits), however induced, was the spleen parenchyma as soft or as moist as in many human cases. In many of these acute splenic tumors, independently of the factor used to produce it, the pulp had a mottled appearance, due to the relatively enormous size of the Malpighian corpuscles which stood out as gray dots. Except for these, the pulp had a dark red-brown color, never the pronounced dirty gray seen in the human gray type. Some variations in color from brown to gray occurred, but the small expanse of surface presented for examination on section of the rabbit's spleen did not make possible a reliable differentiation on this characteristic alone.

The microscopical picture, however, was distinctive, permitting a division into two groups, one produced by organisms giving rise to red and the other by those causing gray acute splenic tumor in human beings. The histological picture of each type corresponded closely, after making allowances for the differences between the normal histology of the human and the rabbit spleen mentioned above, to the corresponding type of human acute splenic tumor.

1. *After Typhoid-Group Inoculation.*—None of these acute splenic tumors, examined at periods varying from three to seventy-two hours after inoculation, and independently of the dose employed, showed the active congestion seen in the corresponding human type, although in the older ones it was more marked than in the earlier. The same increase in prominence and activity of the reticular and endothelial elements was present, with perhaps evidence of phagocytosis

not as marked; and the same diminution of the other cells of the pulp was to be observed. The increase in plasma-cell forms was not so noticeable in rabbits as in human typhoid acute splenic tumors. In addition to these changes, there were large and numerous areas of necrosis, rarely seen in human acute splenic tumors and never to the same extent; and in these areas of necrosis there was regularly a deposit of fibrin, occasionally delicate, but more often dense and sometimes occurring in compact plugs.

2. With *Pneumonia Induced by Intrabronchial Pneumococcus and Streptococcus Inoculation*.—As was noted in those previously discussed, none of these acute splenic tumors, examined at periods varying from five to fifty-four hours after inoculation, showed an advanced grade of active congestion. They were, however, often as much congested as those induced by strains of typhoid organisms in rabbits killed at corresponding periods after inoculation (Fig. 3). None of them showed swelling or proliferation of the reticular or endothelial elements, and all, particularly those induced by intratracheal inoculation of streptococcus strains, presented evidence of hyperactivity of the other cells in the pulp, and especially the myeloid elements, as evidenced by the increased number of oxydase cells. No areas of necrosis were seen in the acute splenic tumors induced by these organisms. In contrast to the human gray acute splenic tumors, the plasma-cell forms were increased as much in this type as in the rabbit typhoid spleens.

II. ACUTE SPLENIC TUMOR ASSOCIATED WITH A STERILE PNEUMONIC EXUDATE.

Several animals were inoculated intrabronchially with a sterile 33 per cent solution of egg-yolk in neutral broth. Such a procedure gives rise to a cellular pneumonic exudate with a functional demand for cells and without any general bacterial intoxication. In the spleens of these animals, studied at periods varying from ten hours to four days, there was a mild grade of active congestion with some increase in size (Fig. 3) which, although much less than that seen in the spleens of the infected animals, could be interpreted from the gross as acute splenic tumor. Microscopical study revealed an increase in the pulp cells, as seen in the spleen accompanying the pneumonia induced by bacteria.

III. RED ACUTE SPLENIC TUMOR IN ALEUKEMIC ANIMALS.

To determine whether the characteristic histological details of red acute splenic tumor, interpreted as showing an inhibition of the leucopoietic tissue of the pulp and stimulation of the reticulo-endothelial elements, can occur in the absence of the hæmatopoietic cells of the spleen, animals were inoculated with typhoid cultures, as above outlined, after poisoning with benzol. All these spleens, although only slightly enlarged above the normal (Fig. 3), were larger than those of animals similarly poisoned with benzol. They were soft, and the pulp was moist and of a dark brick-red color. Under the microscope the venous sinuses were seen to be congested. Owing to the great diminution or complete absence of the

other cells of the pulp and the resulting relative increase in the reticulum and endothelial cells seen in the spleen in benzolized animals, the interpretation of the splenic reaction in these animals after inoculation with typhoid cultures was difficult. The reticulum and the endothelial cells are, of course, prominent, much more so than in animals inoculated with typhoid cultures alone, or only poisoned with benzol. They are markedly swollen and show some evidence of proliferation. Phagocytosis, although not striking, is present. It is noteworthy that the plasma-cell forms, often seen abundantly in human red acute splenic tumor and in both types of acute splenic tumor in rabbits, are relatively scarce in these preparations.

IV. FAILURE TO PRODUCE GRAY ACUTE SPLENIC TUMOR IN ALEUKEMIC ANIMALS.

To determine if the histological changes characteristic of gray acute splenic tumor, interpreted as being entirely dependent on a stimulation of the leucopoietic cells of the pulp, can occur in the absence of the hematopoietic cells of the spleen, pneumonia was induced in animals rendered aleukemic by benzol administration. The inoculations were made on animals with white blood counts on the day previous to inoculation of 600 to 1900. With completely aleukemic animals the bacterial toxins kill too quickly to allow of the development of any splenic reaction. One animal, however, with a white blood cell count of 600 lived six hours after inoculation, long enough for the development of some acute splenic tumor in an animal not poisoned by benzol. The spleen of this animal showed no congestion, but exhibited the collapsed collection of endothelium and reticulum seen in completely benzolized animals (Fig. 3), without infection. Other animals with white blood cell counts less than 2000, similarly inoculated and autopsied after longer periods, showed only the changes in the spleen for animals thus poisoned, and practically no congestion.

V. CHANGES IN THE BONE-MARROW.

The study of the bone-marrow in these experiments was instructive. The myeloid hyperplasia of the bone-marrow in conditions showing the gray acute splenic tumor, and the necroses, myeloid aplasia and prominence of the reticular elements in those showing the red acute splenic tumor, have already been noted in human cases.²³ Similar observations were made on the bone-marrow of these rabbits with experimentally produced acute splenic tumor. In the typhoid animals the histological changes in the bone-marrow were identical with those in the spleen—aplasia of the myeloid elements, numerous and extensive necroses and swelling of the reticulum cells with some phagocytosis. In the pneumonia animals hyperplasia of the bone-marrow was to be observed, slight in some, advanced in other cases. In some, although not in all of these animals having acute splenic tumors, the bone-marrow was congested. The presence or absence of this congestion of the bone-marrow seemed to bear no relation to the substance used to induce the acute splenic tumor.

VI. BONE-MARROW CHANGES IN PNEUMONIA IN SPLENECTOMIZED ANIMALS.

After our studies on the character of the pneumonic exudate in the pneumonias mentioned, which has been reported elsewhere,²⁷ pneumonia was induced in animals that had been splenectomized from one hour to two and a half months previously, and the pneumonia exudate was studied at different periods for any quantitative or qualitative change. There was no change in the character of the cells in the exudate at any stage of the pneumonic process. The number of cells seemed to be diminished, but the great variation in this finding encountered in experimentally induced pneumonia in animals with their spleens intact, allows of no deductions from this observation. In these splenectomized animals, however, induced pneumonia was accompanied by more hyperplasia of the bone-marrow, as compared with the normal animals or the pneumonia animals that had not been splenectomized.

These experiments show that in rabbits two types of acute splenic tumor resembling closely the two human types can be induced by similar etiological agents. The primary characteristics are always the same as those of the corresponding human type induced by the same type of infection, except that, whereas a noticeable increase in the plasma-cell forms occurs only in the human red type, in the rabbits it is seen in both. A functional demand for leucocytes, even in the absence of a general bacterial intoxication, can produce changes in the splenic pulp qualitatively similar to those of gray acute splenic tumor, the only real difference being in the lesser degree of active congestion present. The characteristic histological features of red acute splenic tumor can appear after the destruction of the leucopoietic elements; but gray acute splenic tumor cannot be produced after the leucopoietic tissue has been destroyed. Almost identical changes occur in the bone-marrow as are seen in the pulp of the two types of acute splenic tumor; and the conditions that give rise to gray acute splenic tumor, when induced in splenectomized animals, result in greater hyperplasia of the bone-marrow than is present under similar conditions in animals with the spleen intact.

DISCUSSION.

Recognizing in the splenic pulp three great groups of cells^{12, 22}—the reticulo-endothelial elements, the oxydase-containing myeloid and perhaps non-oxydase myelopotent cells, and a large residue of cells other than these above, including lymphoid cells of various types and stages of maturity, and probably undifferentiated erythropoietic cells, the reactions of the spleen in the commoner acute infections admit of enlightening analysis. This analysis indicates that the conditions included under the term *acute splenic tumor* embrace two major reactions, in effect almost opposites of each other. Both these reactions of the spleen are associated with an active congestion, as is to be expected in any tissue reaction, and the gross characteristics of the acute splenic tumor, the size, consistence, and in large part the color, are dependent upon the amount of congestion present. The type of reaction showing the greatest congestion, the red acute splenic tumor seen in

typhoid fever and closely allied infections, is characterized by an inhibition of myelopoietic activity of the pulp, and hyperplasia and hyperactivity of the reticular and endothelial macrophages. That type of reaction regularly showing less congestion, the acute splenic tumor of pneumonia, endocarditis, and other staphylococcic and streptococcic infections, and others, regularly shows evidence of myelopoietic activity in the pulp, with slight hyperplasia of the other cells with the exception of the reticulo-endothelial elements.

One cannot, of course, say that only the reticular and endothelial cells are concerned in red acute splenic tumor, and that the other elements alone are active in the gray type. The phagocytic activities of the polymorphonuclear and lymphoid cells, as compared with the histogenous macrophages, for want of a more specific term designated reticulo-endothelial cells, must be recalled in this connection. The polymorphonuclears, and to a less extent the lymphocytes, are the active phagocytes, the first line of defense, exhibiting phagocytic activity during the first hour after the introduction of the foreign body.^{12, 28} Later the more slowly moving histogenous macrophages take up the struggle, ingesting particulate matter either too large or too small for the polymorphonuclear cells,^{12, 28} any other residue the polymorphonuclears have been unable to handle, and even dead polymorphonuclears loaded with debris that have succumbed in the struggle. In typhoid fever, no doubt, such a process occurs, so that in the early stages before the hematogenous elements have been injured by the toxin, if there is any phagocytosis to be carried on, much is accomplished by the polymorphonuclear cells. And even in the late stages of the disease an occasional phagocytic polymorphonuclear cell is encountered. But later, when the myelopoietic elements are crippled, as they are in typhoid fever, the burden of phagocytosis falls on the histogenous macrophages, those cells which uninjured by one myeloid toxin, benzol, are likewise uninfluenced by another, the toxin of typhoid fever. Owing to indefinite morphological characteristics, all phagocytic cells in the spleen cannot be definitely diagnosed as histogenous or hematogenous. But many can, through their morphology and relations, be recognized as identical with the vitally staining and endothelial cells, and therefore identified as reticulo-endothelial cells. This is demonstrated more satisfactorily in the Peyer's patches of the intestine than in the spleen, for there phagocytosis, because of the greater amount of tissue debris, is more marked. In typhoid fever, although it cannot be said that only the histogenous macrophages are active, the characteristic histological picture seen not only in the spleen but also in the bone-marrow, lymph glands and follicles, is dependent on the phagocytosis exhibited by these cells.

Similarly, in gray acute splenic tumor, it is not the hematogenous cells alone that are active. On hypothetical grounds some phagocytosis of the histogenous elements is to be expected, and does occur. But because of the slight amount of tissue debris present in the spleen in these conditions, and because of the unimpeded activity of the hematogenous cells and even increase in number, the activities of the histogenous

cells are not conspicuous, and it is the hematogenous cells that have to do with the characteristic features of the histological picture in the gray acute splenic tumor.

It seems probable that the general bacterial intoxication has much to do in bringing about the reactions seen in the spleen. In infections giving rise to acute splenic tumor of the red type, the inhibition of the myelopoietic functions in the spleen and bone-marrow is probably entirely of toxic origin, but the increase of the reticulum and endothelial cells may be a functional hyperplasia. The stimulation of the myelopoietic functions of the splenic pulp and bone-marrow in conditions associated with gray acute splenic tumor is in large part a functional hyperplasia, as evidenced by the production of practically identical changes by a simple demand for cells without any bacterial infection. That such a functional demand for myeloid cells is responsible for the changes mentioned in gray acute splenic tumor seems evident from the fact that they do not appear when the myeloid tissue is destroyed by benzol, and that infections giving rise to gray acute splenic tumor, when induced in splenectomized animals, are accompanied by more than the usual bone-marrow hyperplasia. On the other hand, the characteristic histological changes of red acute splenic tumor are entirely independent of the myelopotent tissue, for they can occur after the destruction of this tissue by benzol. In accord with the statement of Jawein,²⁹ it may be said that the largest acute splenic tumors are those showing active phagocytosis, the red type of typhoid fever; but, in disagreement with him, it seems that this reaction is not dependent solely on destruction of red blood cells. And in the gray type, destruction of red blood cells, or phagocytosis of cellular debris, is not a factor at all in the production of the changes that occur. Although it cannot be denied from the results of this study that myeloid metaplasia of the spleen can result from anemia and blood destruction, it can be positively stated that the myeloid activity of the spleen in the gray acute splenic tumor of some infections is not so caused; but that it is rather a toxic stimulation, as Hertz³⁰ would have it, or more likely in large part a functional hyperplasia.

CONCLUSIONS.

Although this analysis of the histopathology of acute splenic tumor is based upon somewhat fragmentary knowledge of the cellular content of the spleen, it brings further proof that a separation of the vitally staining histogenous macrophages and the endothelial cells from the other cells of the mature organism is justified functionally, although not always possible on morphological grounds; and that the spleen is an integral part of the blood system of the body, responding quickly to any influence inhibiting or stimulating hematopoietic activity. And in regard to the reaction of the spleen in the commoner acute infections it may be said that:

(1) Acute splenic tumors all fall into one or two major groups; the red type, associated with typhoid fever and closely related infections, and the gray type, with pneumococcus, staphylococcus, streptococcus and other infections.

(2) The spleen in each type of acute splenic tumor shows active congestion upon the extent of which depends the size, consistence, and in large part the color of the organ.

(3) The histological picture of red acute splenic tumor is distinctively characterized by hyperplasia and activity, as evidenced by phagocytosis of the reticulo-endothelial macrophages and decrease in number of the other cells of the pulp; and these changes are dependent on a toxic inhibition of the leucopoietic functions of the body associated with typhoid fever, and a stimulation, perhaps functional, of the reticular and endothelial cells.

(4) The histological picture of gray acute splenic tumor is distinctively characterized by an increase in the pulp cells, especially the oxydase-containing myeloid elements, without any proliferation, or increased activity, of the reticular and endothelial cells; and these changes result for the most part from a functional demand for leucocytes.

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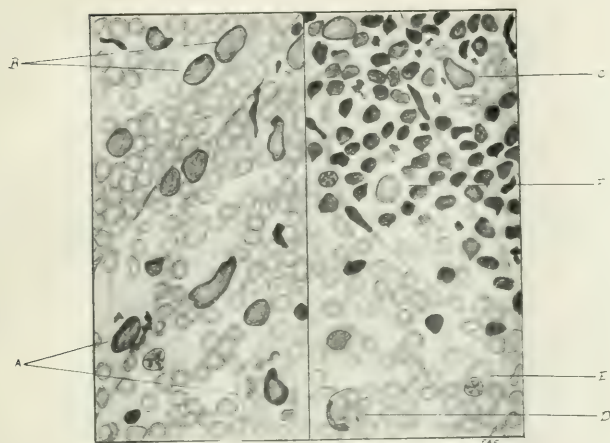


FIG. 1.

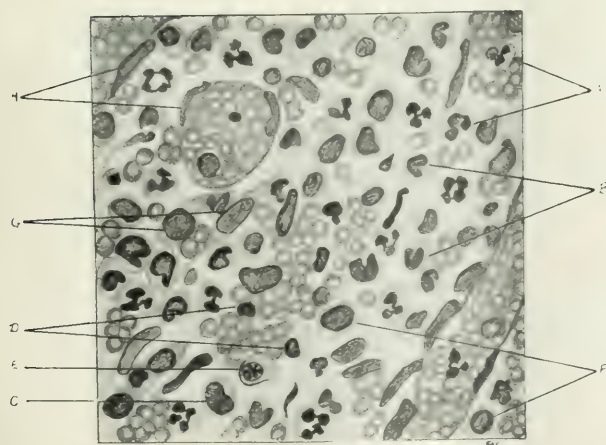


FIG. 2.

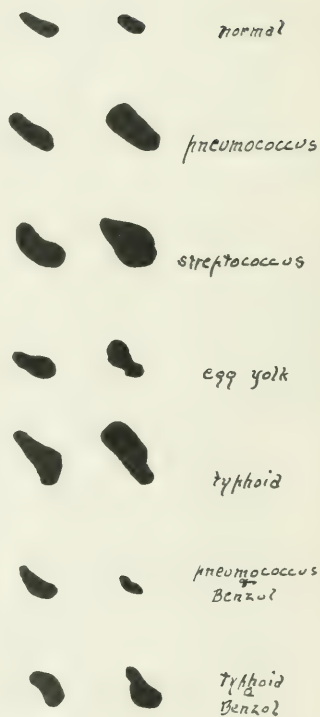


FIG. 3.

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DESCRIPTION OF FIGURES.

FIG. 1.—*Red Acute Splenic Tumor*.—The excess of blood present and diminution in the number of pulp cells is characteristic.

- a. Phagocytic reticulum cells of the pulp.
- b. Swollen endothelial cells of the pulp.
- c. Phagocytic reticulum cell of the Malpighian corpuscle.
- d. Phagocytic cell of the pulp apparently not related to the reticulum.
- e. Plasma cell.
- f. Lymphoblastic cell of the Malpighian corpuscle.

FIG. 2.—*Gray Acute Splenic Tumor*.—The mild congestion and cellularity of the pulp are noteworthy. The endothelium and reticulum cells are swollen, but there is no phagocytosis evident. Polymorphonuclear cells are numerous.

- a. Polymorphonuclear cells.
- b. Oxydase mononuclear cells.
- c. Myelocyte.
- d. Lymphocytes.
- e. Plasma cell.
- f. Non-oxydase mononuclear cells.
- g. Reticulum cells.
- h. Endothelial cells.

FIG. 3.—Cross-sections through the greatest diameter of rabbit spleens, showing acute splenic tumor, and illustrating the variations in size under different conditions. This, in effect, is only a record of the amount of active congestion present.

IRON IMPREGNATION AND INCRUSTATION OF VARIOUS TISSUES.

By OSKAR KLOTZ.

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The presence of iron in calcium deposits has recently had a new importance attached to it in the demonstration of curious bodies believed by some to be fungi. In the intensive researches that have been made upon the various tissues in pseudo-leukæmia, attempts have been repeatedly made to demonstrate micro-organisms as causative agents. Cultural and histological methods have been applied, and in some instances success has been claimed in demonstrating bacterial types. In part, at least, it would appear that the histological methods have been most uncertain, as the development of artefacts, as well as inorganic precipitates, have suggested conclusions which closer scrutiny cannot substantiate.

Recently Sprunt has called special attention to these fallacies. In 1911 he reported peculiar findings in a case of splenomegaly associated with liver cirrhosis. The diffusely fibrosed spleen contained "ocher-colored patches" which on microscopic examination, showed a peculiar pigment about the trabecule and particularly about the blood-vessels. The vessels lay amidst masses of fibrosis, and in the vessel wall, as well as to a lesser extent in the surrounding tissues, were bands and threads of golden pigment. Sprunt was able to demonstrate calcium and iron in these deposits and found that they occurred mainly in elastic tissue. The elastic fibers had undergone various grades of degeneration which they appeared to have a chemical affinity for both calcium and iron. These impregnated salts were readily removed from the tissues with dilute mineral acids.

Subsequently Gibson reported the presence of a streptothrix in the spleens of six cases of "splenic anemia." Four of these cases were of the variety of Banti's disease. In these, as well as in the remaining two cases, he was able to demonstrate threads or strands of yellow line, which he believed he was able to differentiate from tissue structures and recognize as streptothrix infection. Cultures which were made from one case were negative.

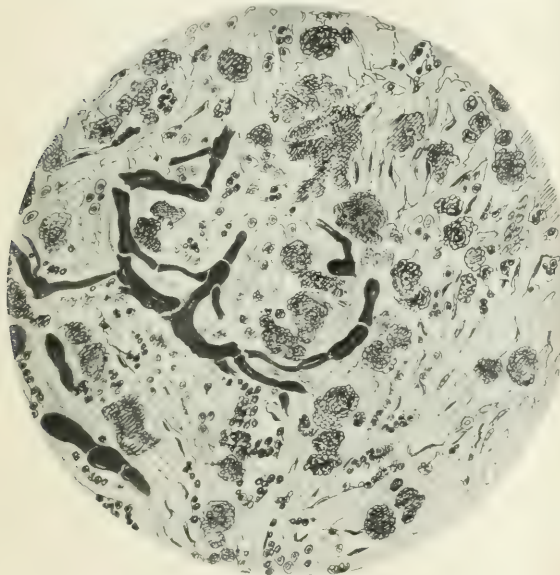
In 1915 Sprunt reported another case of splenic anemia in a man with a history of lues and malaria. The spleen had been removed at operation. Similar pigmented patches were found among the enlarged trabeculae, and microscopic deposits of iron and calcium were demonstrated similar to those in his previous case. Somewhat similar observations had been made in 1902 by Hektoen. He described a process of degeneration in the elastic fibers, with subsequent incrustation with iron salts, in areas of subacute inflammation. These altered fibers were at times incorporated within giant cells. In one of the drawings of these deposits, he shows a structure very similar to the "streptothrix" described by Gibson.

Our attention was called to a similar finding in which, with the application of the simple stains alone, it appeared that we were dealing with a streptothrix and with the smudged masses of the lymphocytes.

The specimens were obtained from a man 46 years old, who for several years had suffered from diabetes. At autopsy, the case illustrated one of the most striking examples of the nature

chromatosis had involved many organs. The most marked deposit of the rusty pigment was found in the spleen, mesenteric lymph nodes, liver, pancreas and heart. As the case will be more fully discussed in a study upon bronzed diabetes, I shall not go into the details of the history or the pathological findings, save those of the spleen and lymphatic glands.

The spleen was of normal size and its capsule was thin and somewhat wrinkled. The tissues were flabby and on section they appeared quite dark with occasional rusty areas. The Malpighian bodies were visible. The pulp substance was not easily broken, but there was no definite evidence of fibrosis. The rusty areas were few in number and consisted of small irregular patches. No direct association of these areas with vascular channels could be made out.



CALCAREO FERRUGINOUS DEPOSITS IN LYMPH GLAND.

The mesenteric lymph nodes and particularly those about the head of the pancreas were a little enlarged, soft and tough. Each node was of a rusty brown color. The tissues about these lymph glands showed no evidence of pigmentation.

The lymph nodes on section showed a diffuse fibrosis throughout their structure and a peripheral thickening of the capsule. Unusually heavy trabeculae entered the gland from the capsule inwards; thus the more marked fibrosis was in the periphery of the gland. The follicular arrangement of the node had been lost and the lymphocytic elements were scattered diffusely without arrangement between the trabeculae and the reticulum. Where the fibrous tissue was laid down in heavier masses it had a very hyaline appearance and showed very few connective-tissue cells. Scattered throughout the gland structure was a heavy deposit of golden-brown pigment. This pigment was granular, varying from fine irregular dust-like particles to

larger aggregated masses formed by the welding together of many small granules. The greater amount of the pigment lay free in the interstices of tissues, but some of it had been phagocytized by endothelial cells.

Aside from the remarkable deposit of granular brown pigment which was found to be iron-containing, there was also a unique appearance in the hyaline trabeculae. In places a deposit of the iron-containing pigment was found within the clefts of this tissue. The deposits were molded into intricate forms identical in appearance with a coarse mycelium or the strands of a streptothrix. These structures showed beautiful transverse segments and not uncommonly club formation at the ends of the strands. In several places, however, one could still make out the individual granules entering into the formation of the more solid segmented strands. Branchings were frequently present, so that divisions, somewhat comparable to those of the penicillium, were found.

Although it appeared evident that all of these fungus-like structures had a common mode of origin, it was evident that some had undergone changes in their composition. Where these molded strands were in process of formation, their character was similar to that of the individual iron-containing granules which were diffusely scattered in the gland tissue. The Nishimura tests for iron were positive, both for the individual granules and also for the streptothrix-like structures. There was, however, some difference in the intensity of the reaction, in that the molded strands were of a lighter color, even blending into a greenish yellow. Furthermore, it was found that with the ordinary hematoxylin stain, irregular masses (by no means all) of the streptothrix-like strands gave a dark purple reaction, which shaded off into a lighter wine color. Some of the strands did not take the hematoxylin stain. Likewise, too, the application of aniline stains led to a partial coloration. The structures, however, did not stain by Gram's method. With silver nitrate a great number of these structures became black and were sharply outlined from the surrounding brown granules. When sulphuric acid was used, a few acicular crystals of calcium sulphate were formed. From the use of dilute mineral acids no gas bubbles were obtained. After the removal of the calcium and iron there remained a transparent hyaline matrix.

Besides these curious structures, there were other linear masses which could be distinguished from those above described. Whereas the former were found to occur in the interstices of the hyaline stroma, the latter had their origin within the more solid structures, at times in the vicinity of blood-vessels. In these there was a primary change of the tissue-matrix with a varying deposit of calcium salts. In these, fine elastic fibrils that coursed through the tissue stroma were demonstrated by Weigert's method, and evidences of varying degrees of degeneration with more diffuse staining of the fibers were obtained. They entered into the tangled structures in which calcium salts were readily demonstrable. In these calcified strands one could not see any pigment granules, and with ordinary or elastic-tissue stains one could not recognize any coloring suggesting an iron-content. Here again, however, the

Nishimura test showed the presence of a diffuse iron reaction, as if the iron salts had been diffusely absorbed in these areas of calcification.

Although it was noted that elastic fibrils in stages of degeneration entered into the bands of ferruginous calcification, these could not be demonstrated in all instances. At times the thickened trabeculae of the lymph gland showed a homogeneous hyaline character which, with the elastic stains, gave a diffuse and relatively pale reaction. Frequently no true fibrils were present, but only a washed or blotchy elastin reaction was obtained. In these areas iron was commonly demonstrated and occasionally small granules of calcium salts.

Similar structures were observed in the spleen. These in part were aggregated in the trabeculae about the blood-vessels and were like those described by Sprunt. Others, found in narrow spaces in the pulp substance, resembled more closely the segmented masses observed in the lymph glands and described by Gibson in one of his cases.

It is evident that in the above case we are dealing with two different kinds of calcium and iron deposits. On the one hand, we have a primary deposition of calcium in elastic fibers with a secondary absorption of iron. In these instances, the deposit of calcium is more extensive than that of iron, and many calcified strands can be found in which iron is not demonstrable. Wherever calcium impregnation of the elastic fibers is noted, a preceding process of degeneration can readily be made out.

The other deposit appears to have no relationship to a primary calcification of tissue structures. Here we are dealing with an unusual abundance of iron-containing pigment which lies in the tissue interstices and gradually becomes molded within the spaces. Wherever the neighboring masses incompletely fuse, evidence of apparent segmentation becomes prominent. Thus chains, like threads of large bacilli, are formed. In these structures, the appearance of calcium salts follows the fusion of the iron-containing granules. No calcium was demonstrable in the original granules and it was only seen in those masses which had fused into clear yellow threads.

The material we were dealing with had been fixed in formalin, and to it the criticisms of Hueck might apply. Hueck claimed that the presence of iron in areas of calcification or in bone, as was demonstrated by Gierke, was the result of an artefact; he claimed that either the fixative contained impurities of iron or that the solution of hæmoglobin in the fixative would tend to deposit its iron constituents in the calcified areas. However, under the conditions of the disease here studied (bronzed diabetes), in which enormous quantities of iron-containing pigment were diffusely deposited in the tissues, the opportunity for impregnation of the areas of calcification before death was constantly at hand. Moreover, the precipitation of iron-containing granules, which became closely massed and eventually formed aggregated cylinders, led to a foreign body mass in which the iron constituent was a prominent part. Under what conditions the calcium salts were attracted to these deposits is not clear, but it was evident that it was a late occurrence.

Our interest in this subject was further aroused by observing the simultaneous deposit of iron and calcium in the arteries. The calcified plaques of the aorta were examined in five cases with negative results. The peripheral scleroses with calcification (iliac, femoral, tibial, splenic) were also analyzed in 10 cases, and three of these were shown to have a deposit of iron within areas of calcification. These deposits are of interest in indicating that the iron had originated from the blood. Two of the specimens were obtained from elderly individuals (64 and 65 years) having senile gangrene of the foot, and one from a man aged 35 years having diabetic gangrene of the foot and leg.

Advanced processes of calcification, and areas where the degenerative process in the arterial wall acts as an irritant, not uncommonly show the development of a granulation tissue about their periphery. The capillary vascularity of these areas varies greatly, and where the stroma is loose small hæmorrhages are prone to occur. This we observed about the medial calcareous masses in each of the arteries obtained from the cases of senile gangrene. Not only did the border of the calcium deposit show the presence of granulation tissue, but an osteoid structure was also present at various points about the mass. Amidst the capillaries was a loose fibrous stroma in which more or less blood pigment was also demonstrated. In two cases the calcium deposits had, for the most part, involved the media, while lesser masses were found in the intima. In all three, calcified elastic bands were found in the zone between the intima and media, and others showing a similar degeneration were scattered between the muscle fibers of the media. An iron reaction was obtained in the calcareous deposits of the media as well as in the brittle elastic fibers associated with this degeneration. In the areas of advanced calcification the reaction was quite diffuse. The deposits of blood pigment and the neighboring elastic fibers also showed the presence of iron.

The third artery showed plaques of calcification in the thickened intima, while the original lumen was occupied by an organized thrombus. Vascular spaces were still present in the organized mass, while in the more solid areas of fibrous tissue deposits of blood pigment, representing the remains of the former blood clot, were readily recognized. Some of these pigment deposits were close to the calcareous masses. On application of the test for iron, not only was a positive reaction demonstrated in the deposits of blood pigment, but a diffuse reaction, more intense in the periphery, was also obtained in the calcareous plaques and in the calcified internal elastic lamina.

In these calcified structures the reaction showed that the iron was present diffusely and in granules. There was no evidence to indicate that the process of calcification had followed the deposition of blood pigment, or that the iron had been obtained from the tissues in which the calcium salts had been precipitated. Many calcified elastic fibers were seen in which iron could not be demonstrated. On the other hand, no iron-containing elastic elements were found in the absence of calcification.

In all of the cases here reported the deposit of iron occurred in calcareous masses under conditions in which there was a

local or systemic destruction of blood. In all instances the blood pigment (hæmosiderin) was deposited directly in the tissues, in which subsequently a mixture of iron and calcium salts was found. Similar observations on the impregnation with iron of tissues about old hæmorrhages have been made by S. Ehrlich and others. The presence of iron impregnation, through the agency of blood iron, in areas of previous calcification is in itself not unique. Whether, however, elastic fibers of arteries and organs may, in the absence of calcareous degeneration, absorb iron, as has been suggested by others, was not definitely determined in our material. It is, however, important that the development of pseudomycelial structures

through the fusing of masses of blood pigment be recognized and distinguished from infecting micro-organisms. These fungus-like structures receive their calcium component late in their development, and many were found without this element.

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NOTES ON NEW BOOKS.

What to Eat and Why. By G. CARROLL SMITH, M. D., of Boston, Mass. Second edition. Thoroughly revised. Cloth, \$2.50 net. (Philadelphia and London: W. B. Saunders Company, 1915.)

Dr. Smith says in the preface of his book: "If 'What to Eat and Why' simplifies dietetic therapy for the medical student and makes it chief among therapies for the busy practitioner, stimulating him to prescribe a dietetic therapy as readily as an electro-, hydro-, serum or drug therapy, the gap I have observed will be filled."

A thorough knowledge of disease and an intimate acquaintance with the physiological and pathological physiological action of foods in the body, both in the alimentary canal, as well as after absorption, are the requisites for any physician who wishes to practise dietetic therapy successfully. The mere prescription of "a dietetic therapy as readily as a drug therapy" will not further the idealistic aims of most physicians or accomplish the greatest amount of good.

In the book at present under consideration, so much has been left unsaid, that the subject becomes extremely simple. This extreme simplicity, however enticing it may be to those looking for practical information in this field, entails slipshod methods that will not be crowned with success. Careful diets, in which the caloric values of all the foods, as well as the proportion of the fats, proteins, carbohydrates and alcohol are painstakingly tabulated, are not furnished in as great a profusion as the modern treatment of obesity, diabetes, typhoid fever, etc., demands. Such qualitative diets as are given under nephritis, in which half of the articles of food mentioned are eggs, meat or fish, and yet the directions call for a limitation of protein intake, suggest that possibly all of the diet lists have not been thoroughly considered. The disturbance of function upon which the principles of dietetic therapy depend are taken up one by one and are fairly inadequately discussed. Very loose statements, as, for instance, that the tendency to gout, obesity, diabetes and arthritis, is increased by the excessive use of alcohol, coffee and tea, also by grief, financial loss, worry, or depressing weather; as well as others that are erroneous, for instance, that metabolism is diminished by the drinking of large quantities of water, are frequently found.

The contents, as well as the title of "What to Eat and Why," are designed to appeal to popular demands. The book will not fill the need of those desiring a well-balanced knowledge of either theoretical or practical dietetics.

H. O. M.

Pathological Technique. By FRANK BURN MALLORY, A. M., M. D., and JAMES HOMER WRIGHT, A. M., M. D., S. D. Sixth edition. Revised and enlarged. 536 pages. 174 illustrations. Price \$3.00. (Philadelphia: W. B. Saunders Company, 1915.)

The invariable presence of this book on the shelves of laboratory workers in pathology and bacteriology attests its usefulness.

By the selection of anatomical and bacteriological methods which it contains, the volume makes available the critical assistance of its experienced authors, and by a combination of lucid diction with intelligent typography it presents its information in the most accessible manner. In the past, the authors and publishers have been felicitated upon this book; a new measure of praise may be added in appreciation of the present edition.

The chapter on Bensley's methods for demonstrating mitochondria and cytoplasmic granules will be welcome to those who are interested in the newer studies of cellular states. The section on bacteriology and parasitology, with its additional paragraphs on blastomycosis and streptothrix, brings this very satisfactory part of the book well up to the needs of the present lines of investigation.

Critical examination of the text reveals only a few incorrect statements and not many errors of omission. Among the former the line on page 66 may be mentioned for correction, where the words "pulmonary vein" are used instead of "pulmonary artery," in the description of the ductus Botalli. On page 137, the authors advise the use of "sterile defibrinated blood" for the preparation of blood agar. A simpler and more satisfactory method is the older one of Schotmüller—in which the blood is drawn into a 2 per cent solution of sodium citrate and thence poured into the agar-medium. The paragraphs on the Widal or "clump reaction" for the diagnosis of typhoid fever as set forth on pages 167-169 would be more adequate if they contained definite reference to the dilutions of serum to be used. The authors consider agglutination of organisms by a serum diluted 1 to 50 as a specific reaction. Many authorities, however, set 1 to 100 as the necessary titer of such a reaction. The section on the cultivation of typhoid bacilli from the feces (page 170) could be improved by a description of Russell's medium. The use of Russell's and Endo's media has given great satisfaction in this laboratory in the differentiation of intestinal organisms.

On page 476, the authors advise the use of the Noguchi butyric-acid reaction in testing spinal-fluid globulin. Most laboratories, in practice, employ either the Pandey or the ammonium sulphate test (the so-called Ross-Jones test) for this purpose. These tests are as satisfactory as the Noguchi reaction, and have no disadvantageous odor.

The last 69 pages of the book contain an assortment of paragraphs on methods for the examination of various materials—from the investigations to be made for animal parasites in the blood and feces to the technique of serological reactions. This compendium of what is known as clinical microscopy is under the caption "Histological Methods"—which is the title at the top of each page of this section. Few of the methods, however, are histological, and some of the descriptions are not sufficient to impart the whole method discussed. Among the latter may be mentioned those on

the Wassermann reaction and Lange's gold chloride test. The description of the Wassermann procedure, written by Drs. Hillman and Burgess, is admirably concise, but it is doubtful whether one without considerable experience could find these paragraphs of great value. Their presence in the book suggests the possibility of their being included in order to popularize the treatise, at a time when there is a general tendency to regard any practitioner as competent to conduct these intricate tests. The obvious dangers of false conclusions which may be drawn by men who have been emboldened by a too facile explanation to attempt the performance of these reactions urge that precautionary statements should be emphasized in these relatively brief outlines of the procedures. Serological methods, moreover, have no place on pages devoted to histological methods. Possibly it would be better if parts of this section were distributed in the general matter on parasitology, under appropriate headings, or separated in an appendix.

S. B. J.

A Treatise on the Principles and Practice of Medicine. By ARTHUR R. EDWARDS, A. M., M. D. Third edition. Thoroughly revised and rewritten. Cloth \$6.00. (Philadelphia and New York: Lea & Febiger, 1916.)

In this third edition of his book the author has effected a reduction in the number of pages and incorporated the advances in clinical medicine since the last issue. The large space devoted to therapy reflects the trend of interest in this direction and also the author's personal views and experiences. This personal side of practice forms the principal excuse for the multiplication of text-books essentially alike.

T. R. B.

The Basis of Symptoms, the Principles of Clinical Pathology. By DR. RUDOLPH KREHL. Authorized translation from the seventh German edition, by A. F. BEFIELD, PH. B., M. D. Third American edition. Cloth \$5.00. (Philadelphia and London: J. B. Lippincott Company, 1916.)

The reappearance of Krehl's invaluable "Pathologische Physiologie" in a new and enlarged translation of the seventh German edition is evidence of the well-merited approval it has won from the profession in America. The new title harks back to the first German edition and draws attention to the practical character of the work.

Dr. Hewlett, who was the first to translate this work into English, and who saw the second American edition through the press, writes a preface to the present volume.

The importance of physiological thinking and the recognition of disturbed function as the basis of symptomatology are hard to overemphasize; and American teachers and students are recognizing these facts more broadly each year.

Krehl's book is without a peer in this field; and this new edition in English brings it up to date and has incorporated in it much of the latest work of our own investigators.

The text is good and the literature well arranged in sections. Every thoughtful student and practitioner will wish to have it in his working library.

T. R. B.

Surgical Operations with Local Anesthesia. By ARTHUR E. HERTZLER, A. M., M. D., PH. D., F. A. C. S. Surgeon to the Halsted, Swedish and General hospitals, Kansas City, Mo. Second edition. 327 pages. 173 illustrations. Cloth \$3.00. (New York: Surgery Publishing Company.)

The rapid sale of the first edition covering minor surgery, and the demand for a more complete work upon the subject, covering both major and minor surgical work, has induced Dr. Hertzler to present this second volume, which for completeness as to detail and for its low price places it, we believe, in a class by itself among the text-books upon this most interesting and growing subject.

Dr. Hertzler's vast surgical experience and his work with local anesthesia constitute him an authority upon this subject; and the second edition of his book places within the hands of the doctor a manual which, for completeness and comprehensiveness, particularly recommends it.

The author seems to have overlooked no point of major or of minor importance. The large number of illustrations fully supplement the text; and both the general practitioner and the surgeon will appreciate this work as a reliable guide in their operations under local anesthesia.

A Text-Book of Pathology. By ALFRED STENGEL, M. D., Professor of Medicine, University of Pennsylvania; and HERBERT FOX, M. D., Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania. Sixth edition. Reset. 8°. Cloth \$6.00; half morocco, \$7.50. (Philadelphia and London: W. B. Saunders Company, 1915.)

The fact that this book has gone through five editions is in itself a sufficient evidence of its value. The authors and publishers furnish a product of over 1000 pages, conforming in every way to the usual profusely illustrated and well-indexed text-book of pathology, which at the end of a brief presentation of a topic leaves no doubt in the reader's mind, no room for argument, and no bibliography of the newer or conflicting views on the subject. This is a type of work which attempts to include every phase of the subject, and certainly a "short, readily comprehended, and even somewhat dogmatic, presentation of a subject" is most welcome to many. Such a presentation, however, to be of real value, can only be the product of those who are familiar with every phase of the subject in all of its details; unfortunately, pathology has outgrown the 'one-man' type of text.

M. C. W.

Short Talks with Young Mothers on the Management of Infants and Young Children. By CHARLES GILMORE KERLEY, M. D., Professor of Diseases of Children, New York Polyclinic Medical School and Hospital; Attending Physician to the New York Nursery and Child's Hospital, etc. Third edition. Revised and enlarged. Illustrated. \$1.00. (New York and London: G. P. Putnam's Sons, 1915.)

This is a very excellent little volume. It gives in a concise, clear and fairly complete form sound advice and directions to mothers and nurses as to the management of their infants and young children.

The discussion of the symptoms of disease are simple and clear. Suggestions for actual medical treatment, as is stated in the preface, are avoided, but the advice given is very practical and should help to fill a very definite want of the average mother or nurse.

"What Every Mother Should Know about Her Infants and Young Children," by the same author, published by Paul B. Hoeber, 67 E. 59th Street, New York, is an abstract of the above volume. Although far shorter than the original, it contains all the essential features of the former, and its very reasonable price (35 cents) should bring it into the hands of many who are unable to purchase the larger volume.

Either book should be a valuable addition to the armamentarium of the visiting nurse, dispensary doctor and social worker, in their efforts for the medical education of the masses.

H. W. W.

Differential Diagnosis, Volume II. Presented Through an Analysis of 317 Cases. By RICHARD C. CABOT, M. D. Cloth \$5.50. (Philadelphia: W. B. Saunders Company, 1915.)

In this, the second volume of "Differential Diagnosis," Cabot follows the same plan as that used in the first volume, that is, he discusses in considerable detail various symptoms of importance through an analysis of cases presenting the symptom in question,

317 cases in all being analyzed in this volume. The major portion of the work is devoted to signs and symptoms referable to the abdominal cavity, and the organs contained therein—tumors, diarrhea, dyspepsia, hematemesis, melena, and ascites being considered in this connection. In other chapters he studies by the same methods vertigo, glandular enlargement, swelling of the face, of the arms and legs, hemoptysis, fainting, hoarseness, pallor, delirium, palpitation, arrhythmia, tremor, polyuria and frequent micturition. The cases are presented with the clearness for which the author is distinguished, and in a style which makes the reading of the book a real pleasure. As to its value as a method for teaching students there may be some doubt, but there is no question that it should prove of the greatest help to general practitioners, as well as to special workers in the various fields discussed, in refreshing their minds as to the multiplicity of causes of many of the common symptoms met with, and the importance of investigating every system in the body, however remote from the apparent source of the trouble, before a diagnosis is warranted.

T. R. B.

Diarrheal, Inflammatory, Obstructive, and Parasitic Diseases of the Gastro-Intestinal Tract. By SAMUEL G. GANT, M. D., LL. D. Cloth \$6.00. (Philadelphia: W. B. Saunders Company, 1915.)

In this book of more than 600 pages Gant reviews the subject of the various conditions accompanied by diarrhea, including those

associated with inflammatory or obstructive conditions in the gastro-intestinal tract. After touching upon the method of classification, which is very exhaustive, and calling attention to procedures of value in examination and diagnosis, he discusses the diarrheas met with in various organic diseases, in acute contagious diseases and in various metabolic diseases, the diarrheas in diseases not often encountered by us, such as sprue, hill diarrhea, typhus fever, and various other forms of the tropical or the sub-tropical types. A short chapter is devoted to the diarrheas due to faulty habits of life, and to the various forms due to disturbances in the secretions or in the innervation of the gastro-intestinal tract. Next he deals with diarrhea due to poisonings, paying especial attention, of course, to those due to decomposed foods. A number of short chapters then follow on the various forms of diarrhea met with in the various entero-colitides—tuberculous, luetic, amebic, bacillary, gonorrheal, etc. The chapters on obstructive or surgical diarrheas and the post-operative diarrheas form a very interesting series, and these are followed by four chapters on the different procedures in the surgical treatment of the various forms of diarrhea—cæcostomy, appendicostomy, appendicocæcostomy, colostomy, colectomy, etc. The book has many points of really great value to workers in this field, but is somewhat long and goes too much into detail to be of much value to the general practitioner except as a reference book.

T. R. B.

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